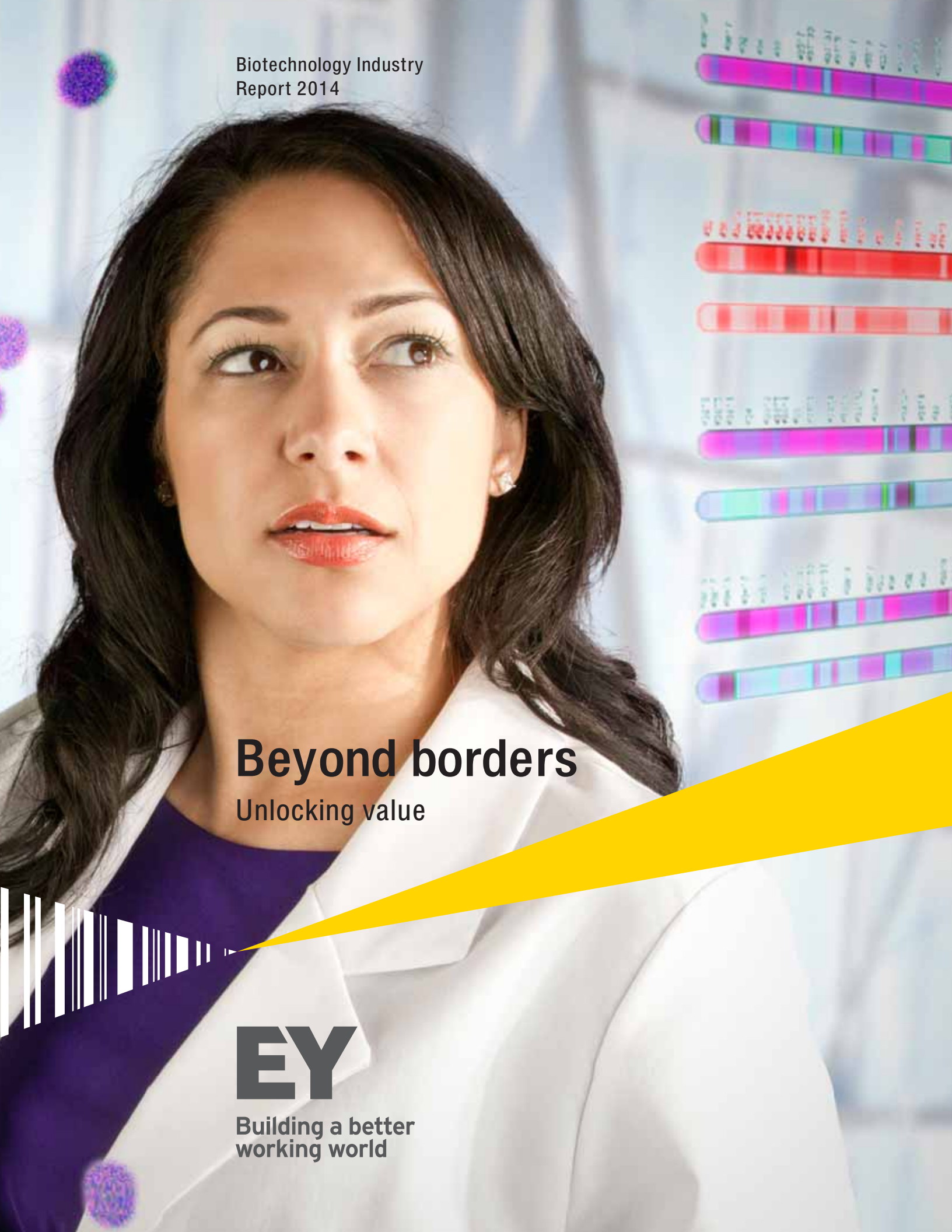
Biotechnology Industry
Report 2014



Beyond borders

Unlocking value

EY

Building a better
working world

To our clients and friends:

A year can be a long time in the biotechnology industry. At this time last year, we were looking back on 2012 and describing an industry preoccupied with squeezing as much efficiency as possible out of a difficult financial environment. The view back to 2013 looks much different. Biotech companies led the way on nearly every metric – deal making, financing and product development. Indeed, they played a key role in new product approvals and important drug launches. Their strong performance galvanized investors, driving the keenest appetite for biotech IPOs since 2000.

But despite biotechnology's remarkable resurgence, the industry cannot afford to be complacent. Resources remain scarce for many. What's more, biotech companies now find themselves in an environment in which payers demand more evidence in order to make reimbursement decisions. Therefore, the need to extract more efficiency from R&D has only risen.

In this, our 28th annual *Beyond borders* report, we examine three strategies we believe enable biotechnology companies to drive efficiencies in R&D and simultaneously generate the evidence that matters to payers. Through adaptive trials, companies can refine hypotheses and reallocate R&D in real time based on data generated in the clinic. Biomarkers allow companies to identify patient subgroups most likely to benefit from a particular therapy, thereby mitigating development risks and potentially increasing valuations from stakeholders. And, participating in cross-industry consortia can help biotech companies better address the many common challenges they face.

To make these strategies work, biotech companies will need to learn new ways of thinking and working. As health care moves to value, and biotech companies move to unlock value, EY's global organization stands ready to help you navigate a path forward.

Join the conversation on our Changing Business of Life Sciences blog (http://lifesciencesblog.ey.com) and through our Twitter feed (@EY_LifeSciences).

Glen T. Giovannetti
Global Life Sciences Leader

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The challenge of recognizing value

The potential for value creation is a central driver of the high-risk, high-reward biotechnology business model. The odds are daunting. But historically, the companies that succeed in bringing breakthrough products to market – and the investors who back them – have reaped handsome returns. In doing so, these biotechs transition from creating value to *capturing* it – generating revenues and earning profits.

The engine driving this value capture is, of course, R&D – the years-long process of identifying and testing via sequential clinical trials. As a product journeys from the laboratory to the marketplace, there are discrete events – for instance, completed phases of clinical trials and strategic alliances – at which key stakeholders step up or down its valuation and/or the valuation of its developer. These inflection points are critical for both companies and their backers, since value can only be captured if it is recognized and rewarded by others.

Financial investors, strategic partners, regulators and payers all play a role in measuring a biotech product's value. However, the ways in which these groups award value are notoriously inefficient – in other words, there is a disconnect between the creation of value by a biotech company and the timing and extent to which this value is acknowledged by other parties.

Traditional drug development methods and business models at least partially account for this lag in value recognition. For instance, the slow and opaque process of clinical trials – in which results are revealed only at a few discrete points – means a company's stakeholders have few mechanisms of measuring and recognizing the value that is being created along the way. And, the single-asset company structures espoused in recent years notwithstanding, most biotech companies are built around a pipeline of assets. This compels investors – who typically prefer to bundle risks themselves – to buy a basket of risks others have created. Unable to accurately ascribe value to a company's pipeline, financial investors therefore assign worth based on sales of marketed products, or – for pre-commercial biotechs – on the future potential of the lead asset.

Recent trends, such as slower market launches and milestone-driven deal structures, exacerbate the issue. As payers more closely examine the value of biotech products, managed entry agreements, in which companies accept more risk and give away more value in exchange for market access, have become increasingly common. Partly as a result of payer pressures, strategic partners have focused on "derisked" assets and deals that include contingency-based payments. Milestones, once based purely on clinical trial results, are increasingly tied to commercial performance. The upshot: as market pressures have increased, biotech companies have been asked to take on more risk while capturing less value.

Matters of evidence and efficiency

In last year's *Beyond borders* "Point of view," we discussed the need for the biotech industry to deal with "matters of efficiency" (conducting R&D and other operations as efficiently as possible) and "matters of evidence" (demonstrating the value of products to payers). Both of these imperatives unlock value. Focusing on efficiency allows companies to use limited resources in the most value-maximizing way, while gathering evidence allows them to capture more value from strategic partners and payers.

As we saw in last year's report, many biotech companies aren't adequately focused on matters of evidence, at least in part because they believe they can't afford the time or capital required to collect the necessary evidence. A critical need, therefore, is to adopt approaches that break this false dichotomy, by providing a way to address simultaneously both matters of efficiency and matters of evidence.

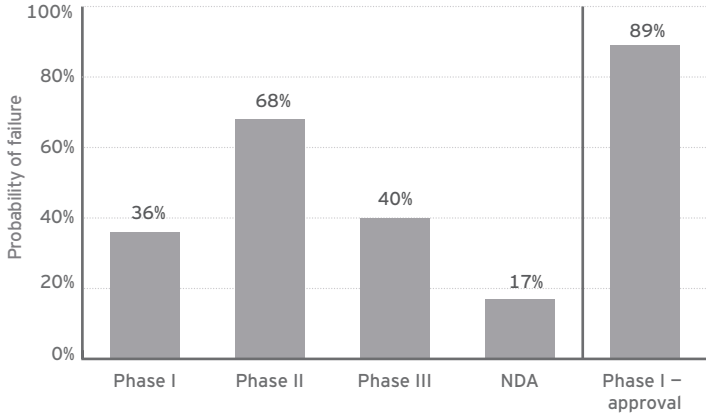
The potential for value creation is a central driver of the high-risk, high-reward biotechnology business model.

Value leakages in R&D

R&D remains a central – if not *the* central – point of value leakage for biopharmaceutical companies. With a few notable exceptions, including Gilead Sciences' hepatitis C drug Sovaldi and Biogen Idec's multiple sclerosis medicine Tecfidera, doubling down on R&D hasn't resulted in drug launches that exceed – or even meet – investor expectations.

Critically, the failure rate for drugs in Phase III is too high – around 40%, according to a team of researchers at Sagient Research Systems and Biotechnology Industry Organization (BIO). From a value-creation perspective, this is perhaps the most inefficient outcome possible. Since the cost of R&D increases sharply from one phase of clinical development to the next, failing in Phase III is a very inefficient use of capital that could have been better deployed on other assets.

Too many drugs fail in Phase III, where R&D spend is highest



Source: EY, Sagient Research Systems and BIO.
Probability of failure was assessed for each stage of drug development, as well as for the entire process (from Phase I to approval).

Three approaches for unlocking value

The discussion above raises four questions with respect to unlocking value:

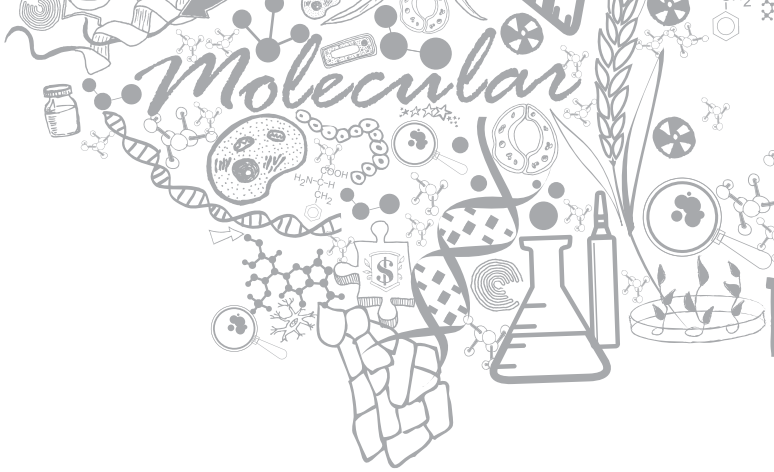
1. How can value be made more transparent for stakeholders, allowing them to recognize value in more timely ways?
2. How can biotech companies recapture some of the value they gave away in recent years because of market pressures?
3. Are there approaches that allow companies to unlock value by simultaneously focusing on both matters of efficiency and matters of evidence?
4. How can capital be used more efficiently in clinical trials, allowing companies' resources to be deployed in ways that create the most value?

R&D remains a central – if not *the* central – point of value leakage for biopharmaceutical companies.

In this article, we focus on three strategies that, taken together, provide potential answers to each of these questions:

- **Precision medicine**, including increased utilization of biomarkers and targeted therapies
- **Adaptive clinical trials**, defined as preplanned alterations, generated via simulations and scenario planning, in clinical trials
- **Precompetitive consortia**, including greater participation in holistic open learning networks (HOLNets)

These three approaches, which can work in tandem and mutually reinforce each other, provide answers to the challenge of unlocking value by pushing different levers. They reduce R&D risk by improving the **probability of success**. They decrease the amount of **capital** committed to R&D, especially clinical trials. They shorten the **time** of clinical development so products reach the market and achieve peak sales faster. And they help increase **sales** of products. In sum, these strategies allow companies to winnow the funnel of R&D candidates to avoid the high attrition rate that currently pervades late-stage drug development. (See accompanying table on page 9).



Unlocking R&D value

Strategy	Opportunity by stage of development		
	Preclinical	Clinical	Post-market
Precision medicine	• Generate important information about a molecule's effect on a biological target	• Identify patients most likely to benefit – or not – from therapy • Identify optimal drug dosage or potential therapeutic risks • Monitor disease status over time • Enable smaller, faster clinical trials	• Allow payers to authorize drug usage in relevant patients • Allow payers to predict drug's impact on health care budgets
Adaptive trial designs	• NA	• Enable more capital-efficient trials • Allow testing of wider range of hypotheses and potential to make real-time modifications based on data • Provide better medical care since patients can be switched from ineffective drugs to those that show promise	• Support collection of data that matter to payers, including against standard of care
Precompetitive consortia	• Identify new biological targets in important disease areas (e.g., anti-infectives, Alzheimer's disease) • Develop new research tools (e.g., cell lines, biomarkers)	• Create standards for new trial methodologies and biomarker development • Share comparator data to make clinical studies more efficient • Operationalize new clinical trial structures to test competing drugs in parallel • Train clinical trial investigators and monitor trial sites	• Devise methods for real-world data capture • Develop recommendations to guide evidence generation required for coverage decisions

Source: EY.

Committing to the development of targeted therapies preserves resources, simplifies the complexity of drug development and speeds discussions with regulators and payers. By recruiting the patients most likely to benefit from therapy from the get-go, companies shorten trial times and lower costs. They may also allow biotech companies to take advantage of the U.S. Food and Drug Administration's expedited approval pathways, including the newly created Breakthrough Therapy Designation program. (For more on expediting drug development, see the point of view by BIO Chair Rachel King on page 30.)

Adaptive trials also create flexibility, enabling companies to test hypotheses *in medias res* via predesignated design changes. Using probabilistic, Bayesian methods, adaptive designs allow companies to target more targets – and to do so more efficiently. In this context, even a negative result – for instance, a drug that fails to exceed a predefined standard – can be a positive, since the company then knows with more certainty the potential risks associated with further development and can act accordingly. The company can choose to shut down the program and redeploy its development budget elsewhere; alternatively, it may design the additional necessary clinical studies or opt to share the development risk with an organization that understands and accepts the gamble.

Based on the individual products in their portfolios, biotechnology companies can tailor the use of precision medicine and adaptive design initiatives as needed. While the advantages associated with these two strategies have been best demonstrated in oncology, at their core, they are disease agnostic.

At a higher level, precompetitive collaborations enable firms to use resources more efficiently. Joining forces, companies solve industry-wide problems, from training clinical trial site investigators to developing methodological standards for capturing real-world data. Sharing resources at this level, companies can invest capital elsewhere.

Recognizing the value of personalized medicine

Mara G. Aspinall
Ventana Medical Systems

Former President

EY: How different are diagnostic regulatory standards from country to country?

Aspinall: Many countries are developing their own regulatory requirements for diagnostics. This is a key issue for drug companies that launch their products globally. As the diagnostic partner, we must also be global and understand the unique needs of each market. It's essential that the drug and diagnostic cross the regulatory finish line together.

EY: How is personalized medicine changing the way health care is practiced?

Aspinall: Today cancer treatment remains organ-based, reflecting realities from before the time we had targeted therapeutics. A patient with lung cancer visits the lung cancer expert; a patient with breast cancer, the breast cancer expert. The molecular underpinnings of cancer have enabled targeted therapeutics, where the treatment decision is based on a genetic signature, not the tumor's original location. In the future, treatments will be best managed by physicians expert in the driving molecular pathway – for example, the expert in ALK or CMET. Tremendous progress has been made moving to this genetically based paradigm, but much remains to be done.

EY: What do those changes mean for Ventana's business model?

Aspinall: First, we have increased research alongside our pharmaceutical partners to develop specific tests that allow physicians to get their diagnoses right the first time, enabling prescriptions that work for their patients. This is not as simple as it sounds. Cancer is a complex disease; multiple pathways play a part in driving any specific tumor, and this mix changes over time, and in response to therapy. Second, we provide the targeted, clinically validated in vitro diagnostics that find the patients most likely to benefit from a therapy. Today we have 188 ongoing projects with 28 different biopharmaceutical companies. Third, and this never changes, Ventana's founding principle is that we make tissue diagnostics precise, accurate, repeatable and cost-effective. We automate tissue analysis and digital imaging to remove sources of all-too-natural human variability, so that it does not matter if your biopsy is done in Boston or Beijing, in a lab that does 20 tests a day or just one a week.

EY: As you do more companion diagnostic work, are the structures of your partnerships changing?

Aspinall: Essentially, the business model is fee-for-service in the development phase today. Once the test is launched, we market it. Getting a more equitable share of the value for the diagnostic from the pharmaceutical partner is challenging. Diagnostic makers and drug developers have completely different business models – different time frames, reimbursement models, risk profiles – and therefore, different profit expectations.

Today, most revenue accrues to the pharmaceutical partner. In the future, I hope we can create broader partnerships where value is equitably distributed between both partners, with, for example, royalties or milestone payments. Smaller, venture-backed companies are in many ways leading the way by already moving in this direction – negotiating risk-sharing deal structures that reflect the value the diagnostic contributes by truly personalizing treatment.

EY: Some biopharmaceutical firms still resist developing and bringing to market targeted therapies. What do you say to these companies?

Aspinall: This resistance has declined dramatically over the past decade. The few holdout drug developers believe that if the drug is prescribed more broadly, revenues will be maximized. This is not the case. A drug that should have been targeted, but was not, will be prescribed for patients that don't respond, physicians will react, and sales will quickly drop below what would have been achieved with a targeted strategy. Ultimately, drug companies want to develop products with staying power – products that truly make a difference in the lives of patients. Companion diagnostics enable that mission.

Of course, information gleaned via consortia can and should inform a company's approach to both precision medicine and adaptive design. As we will discuss, consortia to validate new biomarkers and clinical trial methodologies already exist. When used in concert, biomarkers, adaptive design and precompetitive consortia create a positive and dynamic feedback loop that increases R&D flexibility.

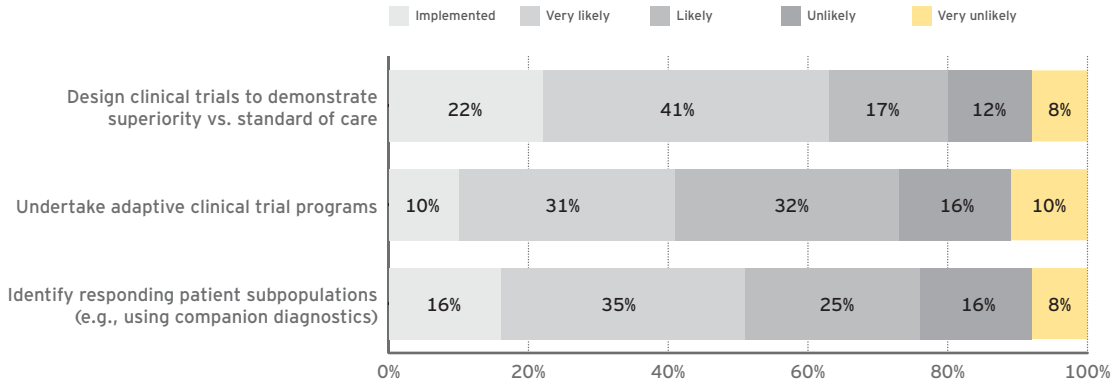
We believe industry executives are aware of the potential advantages biomarkers, adaptive design and precompetitive consortia could bring to their organizations. Roughly 60% of the 451 leaders canvassed in an EY annual survey of biotechs reported being "likely" or "very likely" to adopt biomarker and adaptive design initiatives. That said, fewer than 20% of senior executives surveyed noted they had already implemented biomarker programs or adaptive designs, suggesting points of resistance have prevented their wider adoption. (See chart below.)

What are these points of resistance?

Smaller biotech companies, dissuaded by the resource requirements and the time horizon to recoup benefits, have largely stayed on the sidelines when it comes to participating in precompetitive consortia. As we will discuss, the complexities and higher up-front costs associated with adaptive designs are also barriers to biotech companies that exist on tight budgets. When it comes to precision medicine, the barriers are both tactical and scientific. Although biomarker science has rapidly advanced in oncology, immunology, infectious disease and cardiovascular disease, broadly speaking biomarker identification and validation remain critical areas for further study. When well-validated biomarkers do exist, the added intricacies required to bring a new diagnostic test – or tests – to market in conjunction with a drug on a global scale are not to be underestimated.

To continue to generate the medical advances patients deserve and expect from our industry, it is time to overcome these barriers and acquire the new capabilities that enable companies to capture additional R&D value.

Biomarkers and adaptive trials: plenty of awareness, less action



Source: EY survey of biotech executives.

Chart shows respondents' answers to the following question: "Since the start of the financial crisis, has your company taken, or are you planning to take, the following initiatives?" Average number of respondents: 451. Numbers may appear inconsistent due to rounding.

Betting on biomarkers

It's well accepted that biomarkers provide critical intelligence about whether compounds hit what are believed to be the relevant biological targets and which patient subgroups are most likely to benefit from therapy.

They are also critical in stratifying risk. In the mid-2000s, analysts and investors wrote off Biogen Idec's potent multiple sclerosis medicine Tysabri because its use was associated with a rare brain infection, progressive multi-focal leukoencephalopathy (PML). But with more than US$ 1.5 billion in sales in 2013, Tysabri remains one of big biotech's top revenue generators thanks to a biomarker-based risk-stratification tool the company developed to predict a patient's risk of PML.

"Ultimately biomarkers mitigate drug development risk," says Dr. Glenn Miller, EVP and Chief Technology Officer for MolecularMD, a molecular diagnostic company that partners with oncology drug developers to bring targeted therapies to market. That's one reason MolecularMD defines its business not around diagnostics, but drug approvals. "We want to accelerate the approval process and enhance the probability of success," says Miller.

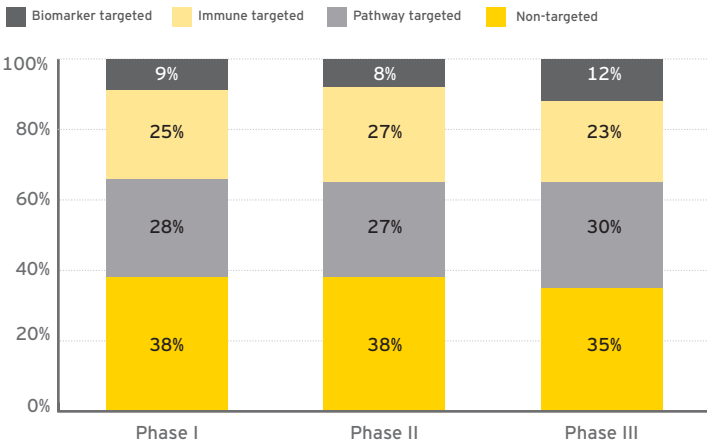
Comparing and contrasting the drug development and regulatory timelines for two different metastatic melanoma drugs – Bristol-Myers Squibb's Yervoy and Genentech (Roche Group)/Plexxikon (Daiichi Sankyo)'s Zelboraf – underscores the advantages of developing a targeted therapy that relies heavily on a biomarker. All told, it took 11 years and a nine-month regulatory review to bring Yervoy to market. In contrast, Zelboraf was developed in just five years and approved by the FDA in 3.6 months, largely because the drug targets a specific oncogene variant expressed only in a subset of patients where there is improved probability of response.

Ultimately biomarkers mitigate drug development risk.

Dr. Glenn Miller
EVP and Chief Technology Officer, MolecularMD

In the past, the commercial bias against biomarkers that stratified patients based on the likelihood of response to therapy meant this type of precision medicine was employed primarily when drugs exhibited poor results in the general population. Why voluntarily limit the population of your drug if it's not required to get the drug on the market?

The biopharmaceutical industry's oncology pipeline



Source: EY, R&D Insight (Adis), press releases and media reports.

In May 2014, EY evaluated 1,212 Phase I, II and III oncology drugs and classified them as targeted or non-targeted. Those classified as targeted were further categorized as follows: biomarker-targeted, immune-targeted or pathway-targeted. Biomarker-targeted therapies affect specific molecular targets (e.g., EGFR, BRAF) and subtype patients. Immune-targeted therapies harness the immune system to attack cancerous cells. Pathway-targeted therapies interact with proteins (e.g., VEGF) or pathways (e.g., Hedgehog, Wnt) known to be important in cancer. Non-targeted therapies are broad-spectrum chemotherapeutics. A handful of immune-targeted and pathway-targeted therapies also rely on a biomarker to identify optimal responders but were not included in the biomarker-targeted category in the above analysis.

Today such an attitude is shortsighted. "Oncology drug makers now need to understand which patients benefit from their drugs and define for providers and payers the patient selection process," notes Dr. Harald Fricke, Chief Medical Officer and Chief Operating Officer for the German biotech Apogenix. "In this context, not having a biomarker can be trouble," he says.

Success stories like Zelboraf and Pfizer's lung cancer drug Xalkori show the potential value of developing therapies that target a subset of patients, particularly in oncology. As of May 2014, drugs utilizing biomarkers to identify patient subpopulations only represent between 8% and 12% of the more than 1,200 drugs in the overall oncology pipeline. (See chart above.)

Capital efficiency in R&D: when more is more

Graziano Seghezzi
Sofinnova Partners

Partner

During the last couple of years, we have witnessed an important "capital efficiency" wave. I have never been a big fan of this approach, because it can have important negative implications for a growing business. Biotech companies, particularly in Europe, often fall into the trap of designing clinical trials to fit their financial constraints. While this may seem like an understandable response to a capital market in which funding remains challenging for many companies, it is actually a more efficient use of capital for start-ups to first outline the experimental designs most likely to give them definitive answers and then calculate how much those experiments will cost.

The most expensive mistake a biotech company can make when investing resources is to underfund studies and end up with an outcome that falls in a classic gray area: promising, but not definitive. In that case, the company has invested significant financial resources – and time – but still doesn't have much certainty about whether its product is truly differentiated.

As an investor, I don't ask companies to be merely capital efficient. I ask the companies I fund to be more efficient with their capital. This small difference in focus has a big impact in how companies operate. Let me give you an example. Sofinnova was the founding investor in Omthera Pharmaceuticals, a start-up developing Epanova, a product for hypertriglyceridemia. As Epanova moved into pivotal trials, the company's board and management team re-examined the proposed study design and concluded that to differentiate the product, additional dose ranges would need to be tested. Clearly this was not the most cost-minimizing decision – it increased our clinical trial costs significantly – but it was the most efficient use of our capital. The data from the Phase III trial differentiated Epanova from its competitors and set the stage for its recent US regulatory approval as well as AstraZeneca's 2013 purchase of the company. Had we not made the additional investment, it's unclear what would have happened to either the product or the company.

Capital efficiency through biomarkers

Another way companies can be efficient with their capital is to use biomarkers across the drug development process. Biomarkers are an excellent tool for managing biological complexity and streamlining early-stage research and development. In particular, biomarkers make it easier to deal with regulatory complexity and provide a rationale for trial choices, including the patient population being tested. That facilitates conversations with regulators. And biomarkers definitely have a role to play at the commercial stage, where they've become essential tools in conversations with payers about product reimbursement.

A biomarker strategy isn't a necessary precondition for every company we invest in. But for certain therapeutic areas, especially oncology, we do believe biomarkers add significant value. Two of our portfolio companies – MISSION Therapeutics and Inotrem – show how.

UK-based MISSION Therapeutics aims to develop novel cancer therapies by exploiting new research on ubiquitin pathways and their effect on the DNA repair machinery. It turns out some cancer cells require specific DNA repair proteins for their continued growth. Inhibitors that block the action of those proteins cause these tumor cells to self-destruct. But the drugs only work effectively in specific genetic contexts. Thus, from the start, MISSION researchers have been focused on discovering biomarkers to identify the genetic signatures that are most susceptible to these kinds of chemical inhibitors. This approach has really simplified the tumor biology research, allowing MISSION to identify several unique drug targets since its inception in 2011.

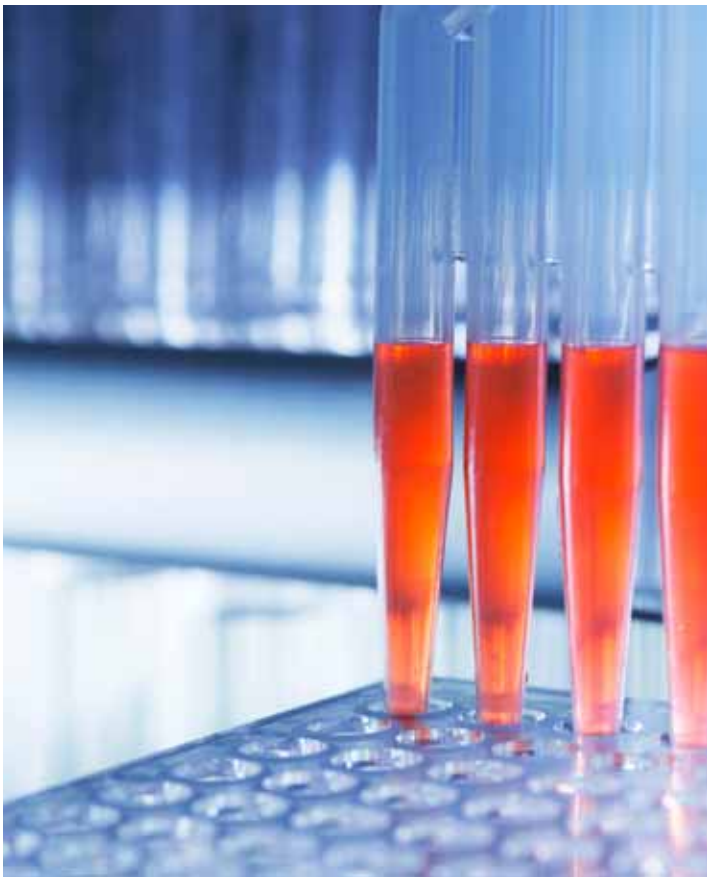
More recently, we invested in Inotrem, a French start-up developing a new sepsis immunomodulator. Sepsis is a risky therapeutic area; the field is littered with novel molecules that have failed in the clinic. But given its incidence – sepsis affects up to 1% of the worldwide population annually and has a mortality rate of 50% – it's an area of tremendous unmet medical need. We felt Inotrem's compound was worth the risk because we saw tremendous promise in the new biology and in the company's strategy to use a biomarker to identify the patients most likely to benefit. In this instance, the use of a biomarker to target therapy played an important role in our investment decision.

Some may worry that biomarkers will diminish drugs' market potential (since they reduce target populations). But the reality is that a targeted drug can have more market potential than one that is not targeted, since payers and regulators want confidence that a product works in the populations in which it's being used. Furthermore, while it's true that prices are being scrutinized more carefully, companies will be better armed for price negotiations if they have truly differentiated products – and one of the best ways to differentiate a drug can be to pair it with a biomarker.

The cultural embrace of biomarkers in oncology is spreading to other disease areas, albeit slowly.

Diagnostic companies are pushing forward to develop independent tests to monitor disease activity in rheumatoid arthritis (Crescendo Bioscience/Myriad Genetics), inflammatory bowel disease (Prometheus Laboratories/Nestlé Health Science) and heart failure (BG Medicine), for instance. Drug companies developing next-generation medicines in these therapeutic areas would do well to pay attention to the emerging research, since use of these biomarkers might provide additional differentiation from existing products. They might also generate surrogate markers that could help speed development and enable expedited approval channels.

Still, according to a study by the not-for-profit National Biomarker Development Alliance (NBDA), only about 100 biomarkers are routinely used in clinical care despite the explosion in biomarker research. As Kristin Pothier, EY's Life Sciences Commercial Advisory Services Leader, outlines in her perspective on page 15, the explosion of technologies and regulatory statutes that transform biomarkers into validated companion tests adds significant complexity to the pharmaceutical business model. Companies must plan in advance on a country-by-country basis their diagnostic development strategies so that access to the accompanying drug isn't imperiled because regulators or physicians question the companion test.



Indeed, companies must understand the nuances impacting the rate at which physicians order companion tests and how payers reimburse for these diagnostics. For now, physicians who practice at community centers don't have the same access to – or potential knowledge about – targeted therapies as physicians who practice at major academic centers. As physician prescribing becomes centralized and the use of clinical decision support tools increases, this situation will likely improve. Physicians will then have feedback on when, and in what patient populations, to use newer tests, including panel tests that can detect hundreds of genetic alterations in a single assay.

The explosion of technologies and regulatory statutes that transform biomarkers into validated companion tests adds significant complexity to the pharmaceutical business model.

On the payer front, the reimbursement climate for diagnostics can be uncertain, especially for tests that aren't directly tied to a therapeutic. That's because in such cases it is harder to make the link between a specific test and an improved patient outcome. Still, there's no doubt that targeting drugs to subpopulations eases conversations with payers, since companion biomarker tests become a mechanism for prior authorization, delineating when a drug is medically necessary for patients.

As Mara Aspinall, the former President of Ventana Medical Systems, points out in an interview on page 10, committing to targeted therapeutics also preserves trust with other stakeholders. Drugs that aren't targeted, but should have been, and subsequently fail to demonstrate efficacy when launched, will not achieve the sales they might have if a precision medicine strategy had been employed. Targeting the medicines from the outset avoids this scenario and ensures the drugs aren't marred by a negative history.

Navigating precision medicine requires going global and local

Kristin Pothier
EY, US

Principal, Life Sciences Commercial Advisory Services Leader

Physicians have promised to deliver the right therapy to the right patient at the right time since the days of Hippocrates. It sounds so simple – in theory. In practice it's anything but.

The use of biomarkers to create targeted, rather than one-size-fits all, therapies is an important step in the direction of precision medicine. Paradoxically, even as biomarkers simplify the complexity of human disease, the explosion of technologies and regulatory statutes that enable their use as companion tests adds significant complexity to the pharmaceutical business model.

Companies have focused on the development of precision medicine in oncology, and development is growing in infectious disease, cardiovascular disease and neurological indications. Those committed to developing precision medicines must ask – and answer – three fundamental questions.

1. **Does the physician know what test to order?**
   In the past, pathologists would diagnose cancer based on cell morphology and tumor location in the body and oncologists would prescribe traditional chemotherapy that killed all rapidly dividing cells, cancerous or healthy. Today, molecular pathologists can analyze the tumor and identify the cancer-causing mutation(s) via diagnostic tests, and oncologists can prescribe therapies targeted to the specific mutation identified. For example, take Xalkori or Zykadia, which selectively affect tumor cells bearing ALK mutations. For patients to receive these therapies, physicians must proactively request ALK testing. In this situation, companies developing an ALK inhibitor must understand whether physicians in a specific market are aware of the accompanying test and perceive its need. They must also understand how the biomarker's prevalence in the population may impact the likelihood that physicians will choose to screen for an ALK mutation over other mutations.
2. **Does the pathologist know what technology is best for testing?**
   Many genetic alterations can be assessed using a variety of molecular testing modalities. For example, ALK mutations can be assayed using one of four different testing methods. A company wanting to launch an ALK inhibitor globally must therefore understand in each geography the pros and cons associated with the technologies, as well as the current and emerging laboratory capabilities, in order to best support routine and accurate testing. Regardless, coordinating such support will require partnerships with solutions providers who have the necessary scientific, analytical and regulatory know-how.
3. **Do the major stakeholders know where the test will be performed?**
   It's not just a matter of plotting the technological capabilities. Screening to identify mutations can be performed in hospitals, outpatient testing facilities or reference labs, and each country has a different approach to this type of diagnostic testing. Companies developing targeted therapeutics have to understand where the testing will take place so they can anticipate hurdles that might reduce test utilization, and thus the volume of patients of the appropriate type being prescribed their drug. For instance, are specific laboratories familiar with the kind of test proposed? Will regulatory or reimbursement statutes limit either the test's availability or its coverage?

The answers to these questions will differ country by country and drug by drug. To execute an effective precision medicine strategy powered by a biomarker, it is imperative that drug makers think globally but execute locally. In other words, they must develop detailed, locally focused implementation plans that specifically take into account physician awareness, access to testing and methodological capabilities on a case-by-case basis.

Devising and executing on such a multifaceted strategy in conjunction with drug development – itself a complicated endeavor – is daunting. Most drug developers, even those who have already embedded diagnostics into their development paradigms, struggle at some point.

To help address these challenges, we assist clients in building strategic go-to-market plans individualized for the specific targeted therapy in question. This includes mapping laboratory capabilities, understanding physician attitudes, assessing regulatory and reimbursement constraints of specific markets, and identifying and evaluating potential diagnostic partnering opportunities. The overriding goal of this approach, of course, is to bring needed therapies to the market faster and more efficiently, with obvious benefits to patients, drug developers and the overall health care system.

The most common adaptive trial designs

Trial adaptation	Description	Advantage	Example (drug sponsor)
Seamless phases of drug development within a single trial	Development phases are combined into single trial (e.g., Phase II-III)	Increases efficiency by reducing time lapses between study phases and eliminating the need to re-recruit patients and create additional study protocols	GENETIC AF (Medtronic/ARCA)
Interim analysis	Trial is stopped or extended based on interim data	Allows earlier identification of ineffective or superior therapies	ASTIN (Pfizer)
Dose finding	Multiple doses are tested over the trial's course	Allows patients to switch to most promising doses, with fewer patients treated at ineffective doses; less likely that the maximum tolerated dose will be over- or underestimated	GSK2586184 Phase II (GlaxoSmithKline); E2006 Phase II in chronic insomnia (Eisai)
Sample size re-estimation	Sample size may be increased following interim analysis	Allows trial to be rebalanced to achieve predesignated conditional power based on interim results	MATISSE (Ziopharm); VALOR (Sunesis)
Patient enrichment	Patient population may be enriched for a particular characteristic after interim analysis	Allows targeting of therapy to patients most likely to benefit	I-SPY (precompetitive collaboration led by UCSF); VS-6063 Phase II in lung cancer (Verastem)

Source: EY and Clinicaltrials.gov.

Finally, applying a precision medicine lens to one's development pipeline enables optionality when it comes time to partner products. Both Apogenix's Fricke and MorphoSys' Chief Development Officer Dr. Arndt Schottelius believe biomarker data increase deal value and help build partnership interest in compounds. "You can always argue that it's too expensive or it's too complicated, but at some stage, such arguments are too little too late," says Schottelius. Fricke agrees, noting that Apogenix is currently holding partnership discussions around its Phase II glioblastoma drug, APG101. "Having a biomarker for APG101 has made the diligence discussion go more smoothly and move more quickly," he says.

In essence, biomarkers allow companies to reclaim some of the value they have been unable to capture in recent years, by making stakeholders – investors, partners, payers and regulators – more likely to assign a higher value to a product. They also give biotech companies more certainty in risk-sharing deals, such as market entry agreements with payers or commercial-milestone deals with strategic partners. In such situations, where biotech companies assume more of the risk related to their products' performance, the use of biomarkers mitigates this risk and increases the ability to capture value by ensuring that drugs will only be used in patients for whom they will likely improve outcomes.

Adapting to new adaptive designs

Committing to targeted therapeutics isn't the only way to narrow the R&D funnel and improve probability of success while shortening development times. Adaptive trial designs, which can be utilized with or without biomarkers, provide similar benefits: they enable companies to refine hypotheses and reallocate R&D dollars in real time based on data generated in the clinic. Moreover, these designs, which can be applied in a variety of therapeutic areas, allow companies to optimize their trial designs based on the parameter of greatest interest, for instance probability of success or speed.

There is no question the current clinical trials paradigm, defined as sequential Phase I, II and III studies punctuated by months of analyses and planning, is outdated. In sharp contrast to the technology and consumer sectors – where big data collected in real time routinely informs product formation – the basic framework for drug development has not changed since the 1960s.

Because of the high cost of late-stage drug failures, companies have tried to curb their development risk by running multiple early-stage studies. The problem is, this strategy simultaneously extends the overall development time for the product and increases costs, but doesn't necessarily provide meaningful data about the probability of success. That's because standard clinical trial designs don't enable companies to test the full spectrum of possible doses or indications and patient populations where the product is most efficacious – at least not without prohibitively increasing cost and time.

I-SPY more innovative trials

Peter Payne
eXcelerate Research

CEO

Dr. Meredith Buxton
I-SPY TRIALS Consortium

Program Director

In 2009, Dr. Laura Esserman (University of California, San Francisco) and Dr. Don Berry (MD Anderson Cancer Center), along with the Foundation for the NIH Biomarkers Consortium, governmental agencies, industry partners and more than 20 academic centers, created the I-SPY 2 adaptive trial to accelerate the development of drugs for neoadjuvant breast cancer. They set a high bar for innovation – a three-fold improvement in time and cost for obtaining regulatory approvals for new cancer treatments.

At the time, there was no precedent for such a fundamental transformation of drug development. To meet its stated goals, the I-SPY consortium, initially sponsored by FNIH and now managed by an independent nonprofit, QuantumLeap Healthcare Collaborative, had to adapt at every level. New organizational efficiencies included: testing drugs by class; developing a "Master" IND and protocol to accommodate testing multiple agents; sharing a control arm across multiple treatment arms; focusing real-time data collection on critical data elements; and utilizing previously and newly developed informatics tools to support next-generation trials.

Initially, the I-SPY 2 concept was not broadly accepted. Some companies were reluctant to participate because of the lack of a clear regulatory path to approval; others questioned whether an academic/nonprofit consortium could execute such a complicated design. Those concerns have since evaporated for two reasons: the FDA issued draft guidance to allow pathologic complete response to support accelerated approval of drugs for neoadjuvant treatment of early-stage breast cancer;[1] and, two agents successfully graduated from I-SPY 2 – Puma Biotechnology's neratinib and AbbVie's veliparib.

Many benefits to I-SPY

We believe there are substantial benefits to our methodology and to this consortium approach to drug development. While a novel trial design may improve the drug development process in one or two ways, we estimate I-SPY has resulted in 10 to 12 advances. In addition, we know Bayesian-designed trials like I-SPY 2 and I-SPY 3 may require fewer patient participants to deliver relevant clinical endpoints. The result is a trial with operating costs estimated to be up to 50% lower than a typical Phase III trial in breast cancer.

We estimate that the two drug regimens that have successfully emerged from I-SPY 2 have a greater than 75% probability of success in a Phase III neoadjuvant trial for the identified biomarker signatures for which they "graduated." Currently, the average probability of success for oncology drugs moving from Phase II to Phase III is around 35%. In addition to greater certainty in pivotal trials for regimens that graduate from I-SPY 2, the adaptive design creates an opportunity for companion diagnostic development and the potential to register a novel drug for significantly less money. This enables smaller, earlier-stage companies to bring drugs to registration themselves, thus retaining an asset's full value.

Separately, the adaptive, biomarker-based trial design enables us to make adjustments based on rapidly changing standards of care and keep pace with innovation in real time. Indeed, in the midst of I-SPY 2, the accelerated approval of Genentech's Perjeta created a challenge in recruiting patients to arms that did not include either it or a new agent. We were able to adjust to emerging changes in treatment in our current trial, as well as in the planned design for I-SPY 3.

Accelerating research via eXcelerate

At the end of 2013, we created a separate entity, eXcelerate Research, to operationalize clinical trial efficiencies. eXcelerate's near-term goal is to further optimize I-SPY to make the process of moving from early to pivotal development as seamless and streamlined as possible. We are assisting in the development of a consortium for a Phase I platform in order to accelerate the pipeline of drugs that move into I-SPY 2 and then I-SPY 3. We are also working to apply I-SPY learnings in diseases other than breast cancer.

[1] Esserman and Woodcock, *JAMA*, 306(23), 2011, pp. 2608-9.

Solution development: a new approach to R&D

Dr. Peter Kolchinsky
RA Capital

Managing Partner

Even as biotech companies profess a desire to develop innovative, breakthrough products, too few are doing so. Unfortunately, many companies set their drug development priorities based on what's solvable with the tools at hand – their capabilities and the most advanced assets in their pipelines. This attitude has led to the development of products that are incrementally better but rarely significant therapeutic advances. You would never hire a plumber armed only with a screwdriver to fix your leaking sink; yet, in our industry, there are many companies hawking screwdrivers because those are the only tools they have.

To jump-start more innovative R&D, we need a solutions mentality. This starts by asking the higher-level question: "what will it take to solve the clinical problem?" To develop remedies that are truly innovative, companies need to construct mechanistically diverse pipelines directed at the same clinical goal, not pipelines of mechanistically similar agents directed to diverse goals. These diverse agents should be advanced in parallel, ideally using what I call multiplexed Phase II trials to establish proof-of-concept.

I call this approach "solution development." Solution development improves the odds that a "winning" drug is not simply a modest improvement over placebo, but also better than other agents. Only the best drug would be advanced to Phase III and, ultimately, the market. Importantly, a company practicing solution development might be able to combine multiple placebo-beating agents into a co-formulated or co-marketed best-in-class regimen.

Testing drugs against one another in a multiplexed trial is not mission-critical for a solutions company since cross-trial comparisons can still be made. What's most important is that a solutions company defines itself by the problem it aims to solve and, like a well-equipped plumber, brings all the necessary tools to the job.

Good examples of companies practicing solution development include Gilead Sciences (HIV, hepatitis C), Roche (breast cancer), Biogen Idec (multiple sclerosis) and Vertex Pharmaceuticals (cystic fibrosis). Novartis and GlaxoSmithKline's recent agreement to swap vaccine and oncology assets better equips each to be solution providers. Small companies, too, can practice solution development. Achillion Pharmaceuticals, Novavax and Dyax have defined themselves in, respectively, hepatitis C, respiratory vaccines and hereditary angioedema.

Changing the conversation

Taking a solution development approach sends a powerful message to patients, payers and investors. A single exceptional drug, a combination approach or a set of agents comprising a continuum of treatment are more likely to offer meaningful benefit to patients with a particular condition regardless of their specific symptoms or disease severity. Companies can then have very different discussions with payers about their products' formulary placements than those offering a single incremental product. Especially in the case of combinations and multi-line regimens, companies could contract with payers across their product portfolios at fixed per-patient per-year prices.

Investors, too, would welcome more solution development compared to the usual options. Investors would judge a solution development company based on the overall probability that it could solve its targeted problem. Against a backdrop of conventional biotech companies with one drug candidate for a particular disease, a well-equipped solution development company will stand out as the one clear bet for those investors who believe solving that particular problem is worthwhile and likely to be profitable.

Toward broader adoption

Solution development requires some uncommon skills and circumstances. For starters, it demands flexible management teams. Clinical teams must be capable of developing products across all technology types – from antibodies to small molecules to RNAi to gene therapy. A head of R&D versed only in traditional approaches isn't perfectly positioned for solution development; nor is a CMO uncomfortable with trial designs requiring double or triple dummy placebos and adaptive statistics.

Finding the right assets isn't trivial either. Most biotechs would consider themselves well positioned if they had one strong Phase II candidate. How could a company get three? Partnering is one obvious way to bring in potential adjacent molecules. Companies could emerge as partners of choice by structuring licensing deals or joint ventures that allow all parties to benefit regardless of whose drug succeeds.

Finally, there are cost concerns. Running a multiplexed trial – or three parallel studies with three candidates – will cost more than a standard Phase II study. Still, economies of scale mean it won't cost three times the amount. Fortunately, there are many examples of investors choosing to contribute toward a large financing that allows a company to take the right development path toward an inspiring clinical and commercial goal.

You are being forced to take a rifle shot when you don't actually know where to aim the gun.

Dr. Frank David
Managing Director, Pharmagellan

"You are being forced to take a rifle shot when you don't actually know where to aim the gun," says Dr. Frank David, the former Director of Strategy for AstraZeneca's Oncology Innovative Medicines unit and now a managing director with Pharmagellan. Companies, particularly smaller, cash-poor entities, are thus forced to test only a small number of hypotheses – or maybe even just one hypothesis. "You are setting yourself up not to create value," David states.

Dr. Peter Kolchinsky, Managing Director of RA Capital, agrees. He believes companies should construct mechanistically diverse pipelines directed at the same clinical goal, preferably advancing agents in parallel via proof-of-concept studies that pit drug candidates against each other. (See Kolchinsky's perspective on page 18.)

Another issue: once allocated, R&D funds are tied up for multiple years with little or no visibility into the investment's potential likelihood of success. This lack of transparency makes it difficult to reallocate R&D funds from riskier assets to drug candidates that are more likely to succeed based on mounting data. Thus, biotech companies and their investors are forced to treat R&D expenses as a sunk cost that is only re-examined as the therapeutic moves through the discrete phases of drug development. In today's world, there is a 40% chance the entire R&D investment is lost for products that advance to pivotal trials.

But imagine if drug developers could more closely link their trial designs to the value of the assets in question based on information that emerges from ongoing trials. Adaptive designs that rely on sophisticated, probabilistic algorithms allow researchers to make pre-planned adjustments to clinical protocols at interim checkpoints. As the table on page 16 shows, a variety of different FDA-endorsed adaptations are currently in use. Depending on the critical issue a company is trying to solve – for instance, improving probability of success or shortening development time – there is an adaptation that can meet its needs.

Consider the following example: a biotechnology company has just finished first-in-human studies of a novel agent to treat a rare cancer. Like many drugs in development today, the unmet medical need this therapy addresses is large, but the commercial opportunity (based on market size) is small. Moreover, there aren't robust biomarker data allowing the clinical team to target the product to a particular patient population. Finally, there are no well-vetted alternatives to the endpoint required for approval, in this case overall survival. That makes it hard to derisk the more expensive, time-intensive Phase III trial via a shorter, cheaper Phase II study. Instead, the biotech would need to run a slightly smaller, but still expensive, version of the pivotal trial in Phase II.

Comparing a traditional clinical trial to an adaptive design

Trial adaptation	Traditional design	Adaptive design
Study size (number of patients)	459	316
Average time (months)	68	34
Probability of success	59%	59%
Trial costs for initial 24 months	US$ 10.0m	US$ 18.1m
Overall trial costs	US$ 35.7m	US$ 26.3m
Adjusted NPV	US$ 5.1m	US$ 34.9m

Source: EY.

R&D costs were modeled for a traditional Phase II-Phase III design and an adaptive Phase II/III including two interim analyses for early success or early termination. EY modeled monthly development costs and sales for both trial designs to calculate an adjusted NPV.

Modeling this scenario, EY's Commercial Advisory Services team estimates an average time (68 months), cost (US$ 35.7 million) and probability of success (59%). But because the cancer's prevalence is rare, the estimated net present value (NPV) and internal rate of return for the asset are just US$ 5.1 million and 3.1%, respectively.

Faced with such numbers, should the R&D team approach executive management and advocate for the resources to push the asset ahead – or is it better to kill the development program and move on to other opportunities? If the team chooses the former strategy, it may be sinking R&D dollars into a program that, if it works, provides a step change in therapy for patients but only a modest return for the company and its shareholders. If the program fails in the pivotal trial, however, precious cash and time have been siphoned away.

Neither option is particularly acceptable.

The table above shows how an adaptive trial design might change the calculus and the R&D decision-making for this asset. By employing a combined Phase II/III hybrid with two interim analyses, the R&D team can avoid duplicating efforts necessitated by the traditional design, shortening the overall time of the clinical trial by 50% and reducing the size of the trial by nearly 30%. Based on EY's analysis, cutting the trial time in half and reducing the sample size results in a seven-fold increase in the risk-adjusted NPV of this hypothetical oncology asset. That's because it both accelerates the product's launch and extends the total time that peak revenues are realized before loss of exclusivity.

Using adaptive design to change an asset's risk profile

Dr. Nitin Patel
Cytel

Chairman and Chief Technology Officer

Historically, biotechnology companies haven't fully appreciated the link between trial design and the ability to secure external financing. Yet, adaptive trial designs – which often reduce the risk, time and cost associated with clinical development – can make the math more attractive for investors and increase the pool of potential financing at a time when raising capital remains challenging for many biotech companies.

Sunesis Pharmaceuticals, a mid-sized biotechnology company client of ours, provides a compelling example of this effect. Using an adaptive trial design, Sunesis was able to derisk its lead asset, vosaroxin, and secure US$ 25 million for the product's development from Royalty Pharma, a New York-based investment firm that provides financing in exchange for a royalty interest in pipeline assets. When the Sunesis deal was signed in March 2012, vosaroxin was being investigated in a Phase III trial for acute myelogenous leukemia – a fairly atypical investment for Royalty Pharma. However, the use of an adaptive trial allowed Sunesis to secure funding from Royalty Pharma in a deal both parties called a win-win.

Sunesis originally considered measuring vosaroxin's efficacy via a traditional Phase III clinical design that required enrolling 450 patients over 30 months. However, at this sample size, there was a very real risk the trial could be underpowered if the true survival benefit was less than the assumed 40%. And adequately powering the study would have required enrolling more than 700 patients, a proposition that was too costly for a broader range of clinically meaningful outcomes.

The approach we suggested, which formed the basis for Sunesis' VALOR trial, was to use an adaptive trial design that included the option to increase patient enrollment by 50% after a predefined interim analysis. Sunesis could stop the trial if there was overwhelming evidence of vosaroxin's efficacy at the interim analysis. On the other hand, if the efficacy results were very weak, the trial would be stopped for futility. If the data were promising, the trial would continue until the company had enrolled 675 patients. The adaptive study design allowed Sunesis to only increase the size of the trial at the interim analysis if the obtained results met a predetermined, promising threshold.

In addition, the stepwise analysis of the data created an opportunity for Royalty Pharma to finance vosaroxin's development while simultaneously hedging its risk. Under the terms of the agreement, Royalty Pharma would commit US$ 25 million to vosaroxin's development only if the VALOR interim analysis did not result in stopping the trial early for futility. If the interim data suggested vosaroxin was unlikely to be efficacious, Royalty Pharma would owe nothing to Sunesis. Moreover, the return to Royalty Pharma – structured as a percentage of net sales – would increase from 3.6% to 6.75% if the interim efficacy was promising and required a trial extension. (Royalty Pharma would also receive warrants to purchase two million Sunesis shares at a strike price above market if the size of the trial increased.)

In essence, Sunesis agreed to this as a way to finance an increase in the size of the trial. The alternative would have been to sell equity at a time when the company felt its stock was under-valued, a scenario that would have diluted its ownership in all of its programs. Royalty Pharma, meantime, reduced its risk by only investing if the intermediate results crossed a specific efficacy threshold, and captured a greater share of future revenues if the riskier scenario – a trial extension – occurred.

Approximately six months after the deal was signed, Sunesis' independent data and safety monitoring board recommended extending the VALOR trial. As *Beyond borders* went to press, Sunesis announced it expects to release pivotal data in the third or fourth quarter of 2014 for vosaroxin, which, if approved, will be known as Qinprezo.

According to Tufts University's Center for the Study of Drug Development, 20% of all clinical trials being conducted today involve some type of adaptive design. Even the simplest designs can have a big impact on R&D budgets. Based on Tufts' estimates, so-called early termination designs and sample size re-estimations used across development portfolios would save sponsor organizations substantial direct and indirect costs. Sponsors would also save money by reducing the number of protocol amendments. Tufts researchers believe that, according to their analysis, each clinical trial amendment results in another US$ 500,000 in direct costs, as well as a 60-day delay for implementation.

Despite such cost analyses, data amassed by the contract research organization (CRO) Aptiv Solutions suggest that other than early adopters such as Merck, Eli Lilly and Johnson & Johnson's Janssen unit, most companies – especially small and mid-cap biotechnology companies – are unaware of how much value adaptive trials bring in the earlier stages of drug development. "It's not filtering down as quickly as it could," observes Aptiv's SVP of Global Strategic Marketing, Phillip Birch.

This lack of awareness also extends to biotech investors, who, if they do focus on clinical trials, are more invested in end-point selection and protocols than overall design. Because adaptive trials enable a more realistic assessment of a product's eventual success, any information that credibly derisks the asset allows new kinds of backers to invest in it. Dr. Nitin Patel, Chief Technology Officer and Founder of the CRO Cytel, explains in an accompanying point of view how its client Sunesis used an adaptive design to derisk its cancer drug and gain funding from investor Royalty Pharma. (See page 20.)

Examples such as this highlight how adaptive trials can address some of the inefficiencies in biotech value recognition identified at the beginning of this article. Adaptive designs empower a company to generate more information about the value it is creating throughout the clinical trial process – not just at a few discrete intervals. They also allow investors to recognize value in more timely ways. As the Sunesis example demonstrates, adaptive trials permit biotechnology companies to slice up their drug development risk in ways not possible via traditional designs where binary outcomes mean the risk profile is either high or low. This reallocation of risk enables investors with certain risk-reward profiles to invest in the risks they find most appealing. This potentially reduces the overall cost of capital to companies since investors are likely to value assets more fairly when the risks specific to the given asset aren't commingled with other uncertainties.

Finally, as adaptive designs evolve, it's likely they will enable evidence collection to justify reimbursement. According to Aptiv's Birch, adaptive designs enable companies to tease out the key elements that define a product's effectiveness. "The data generated can link efficacy to effectiveness," he says. Others point out adaptive designs are a natural fit for comparative effectiveness research since they can accommodate products entering and leaving the market or changing standards of care more easily than standard clinical designs.

Innovation today requires data analytics capabilities beyond those of any one company, any one institution or any one country.

Dr. Elias Zerhouni
President of Global R&D, Sanofi

Open-sourcing R&D

As we discussed in *Beyond borders* 2012, improving R&D productivity requires the creation of open networks that continuously share information – and learn from it – throughout the cycle of care. Within these holistic open learning networks, or HOLNets, a broad spectrum of participants collaborate in precompetitive spaces to share data and define standards. Since 2012, dozens of HOLNet-like consortia have been established to solve common challenges and ensure limited resources are used in the most value-maximizing ways.

These challenges can be scientific or methodological. In the preclinical space, for instance, the dearth of predictive cell and animal models for CNS diseases means it's difficult to adequately assess how a new molecule affects human disease. Similarly, incongruent regulatory standards and outdated methodologies linked to trial design and data analysis have also limited industry's ability to innovate.

Innovation today requires "data analytics capabilities beyond those of any one company, any one institution or any one country," says Dr. Elias Zerhouni, President of Global R&D for Sanofi in a guest perspective that starts on page 32. Zerhouni believes precompetitive collaborations have a role to play throughout the drug development life cycle and has pushed for Sanofi's involvement in a number of different consortia. Most recently, Sanofi has joined the Accelerating Medicines Partnership, whose

members will pool data and expertise in four disease areas, and Project DataSphere (PDS), which aims to improve clinical trial designs by sharing comparator data for oncology medicines. (See the table below.)

TransCelerate BioPharma offers yet another example of how life sciences companies are coming together to develop shared solutions to improve R&D. Like Project DataSphere, TransCelerate aims, via the creation of methodologies and tools, to streamline the operational aspects of clinical research. "It became apparent to senior R&D leaders across the industry that the historical model for clinical trials – from their design to their execution – wasn't sustainable and resulted from legacy practices," says TransCelerate's Chair, Dr. Annalisa Jenkins.

TransCelerate, which launched in September 2012, has expanded from 10 to 19 organizations. The partnership is focused on eight different initiatives, including creating master service agreements that ensure timely access to comparator drugs. As Jenkins outlines in a separate perspective, there is definitely room for smaller biotechnology players to join TransCelerate's efforts. "As we develop new tools, such as investigator registries or methodologies tied to risk-based monitoring, it's important that small biotech companies can implement these solutions just as easily as mid- and large-capplayers," she says.

Importantly, precompetitive collaborations like TransCelerate and Project DataSphere still allow individual companies to compete. But now they are competing where it matters most and where they have the most control: at the individual asset level, where the quality of the science and the depth of the research team can provide significant differentiation.

As we develop new tools, such as investigator registries or methodologies tied to risk-based monitoring, it's important that small biotech companies can implement these solutions just as easily as mid- and large-cap players.

Dr. Annalisa Jenkins
Chair of TransCelerate BioPharma

Selected precompetitive collaborations

Name	Indication/Focus	Founding organization(s)	Goal
Accelerating Medicines Partnership	Alzheimer's disease, Type 2 diabetes, rheumatoid arthritis and lupus	The National Institutes of Health (US), Johnson & Johnson, AbbVie, Bristol-Myers Squibb, Merck & Co., Pfizer, Sanofi, GlaxoSmithKline, Takeda Pharmaceutical Co., Biogen Idec, Eli Lilly, the American Diabetes Association, the Alzheimer's Association	Charting molecular pathways and identifying new biological targets
ADDPLAN DF Consortium	Adaptive trial design across diseases	Novartis, Janssen Pharmaceuticals, Eli Lilly, Aptiv Solutions	Designing and validating new statistical methodologies and execution technologies for use in adaptive trials
European Gram-Negative Antibacterial Engine (ENABLE)	Anti-infectives	GlaxoSmithKline, Innovative Medicines Initiative, Uppsala University and more than 30 partner organizations	Developing novel antibiotics against gram-negative pathogens; bringing one new agent to market by 2019
National Biomarker Development Alliance	Biomarker development across diseases	Arizona State University	Creating an evidence-based biomarker development process that spans early discovery to clinical application
National Lung Matrix Trial	Oncology	Pfizer, AstraZeneca, Cancer Research UK, the National Health Service (UK)	Testing up to 14 lung cancer drugs in parallel using a master protocol and an adaptive trial design based on biomarkers; thematically similar to I-SPY trials for neoadjuvant breast cancer
Project DataSphere	Oncology	Pfizer, Sanofi, AstraZeneca, Bayer HealthCare, Celgene, Johnson & Johnson, Memorial Sloan Kettering Cancer Center	Making available de-identified patient information tied to comparator drugs in late-stage cancer trials

Source: EY, press releases and media reports.

Accelerating clinical development

Dr. Annalisa Jenkins
TransCelerate BioPharma

Chair of the Board

The clinical development process, especially the design and execution of clinical trials, is a core business process that runs through every biopharma company – and it's overdue for an overhaul.

Our current clinical development model isn't sustainable. The way we enroll clinical investigators and qualify trial sites is cumbersome; standards for clinical data aren't well established; and the development costs just keep going up.

Senior R&D leaders across the industry have realized that unless they work together to address systematic, deep-rooted inefficiencies, even the best-funded players won't be able to sustain a return on their R&D investments, causing a decline in the development of new and important drugs.

And so, in September 2012, TransCelerate BioPharma was born.

TransCelerate was hardly the first industry consortium formed to solve a common challenge in the clinical trial environment. But with eight ongoing initiatives and 19 participating member companies, it is one of the biggest and most ambitious. Our overarching goal is to simplify and accelerate the delivery of products to patients by improving the operational efficiencies of clinical development.

In defining our initial priorities, we asked the question: what are the "low-hanging fruit" where common solutions would improve clinical development? As we identified potential projects, we prioritized them based on their ability to increase the quality and efficiency of clinical trials or reduce their costs. Demonstrating the breadth of our goals, our first eight initiatives include the development of common clinical trial protocol templates, shared investigator registries, and frameworks for streamlining the qualification of investigator sites.

We're proud of the results we've delivered thus far. For example, one of the main barriers to more efficient studies is access to comparator drugs and co-therapies because their procurement is unpredictable. To solve this problem, we created a supply network among biopharma companies to establish a reliable source of comparator drugs for use in clinical trials. Skeptics said companies would never collaborate on this initiative. We launched the network in August 2013 with participation from several TransCelerate member companies, and 37 transactions have already taken place.

Developing a common framework for how companies monitor potential safety risks at clinical trial sites is another initiative the industry has discussed for years. But since the effort requires close collaboration with regulators, it's tough to make headway. As a not-for-profit organization, we can engage with US and European regulators in a different way than individual companies or conventional policy-based trade associations. Working with the European Medicines Agency and the U.S. Food and Drug Administration, we've developed a risk assessment and categorization tool to help companies improve their clinical trial site monitoring. Over 40 active studies across member companies are ongoing, testing the framework in specific disease areas.

As TransCelerate evolves, it's important to stay focused on our mission. We will continue to collaborate with other stakeholder groups in the clinical trials landscape, including regulatory authorities, investigative sites and contract research organizations. But we want to avoid "scope creep." And we don't want to invest in areas other consortia are already tackling.

Certainly, we want companies from across the industry to participate. As we develop new tools, such as investigator registries or methodologies tied to risk-based monitoring, it's important that small biotech companies can implement these solutions just as easily as mid- and large-cap players. Companies of all sizes have something to contribute. We are interested in financial resources, of course, but more importantly, we want companies' ideas.

Through our initiatives, we hope TransCelerate engenders trust between the industry and the outside world. For the next 5 to 10 years, senior R&D leaders in all segments of the industry need to collectively reshape the dialogue about the benefits of new biopharma innovations.

TransCelerate is – and will continue to be – an important voice in that conversation.

Translating biomarkers into meaningful tests requires a whole new skill set that diverges from drug development.

Points of resistance – cultural, not scientific

Given the data showcasing the potential for both biomarkers and adaptive designs, why are so few companies integrating these strategies into their clinical development programs? And why are smaller biotech players hesitant to play bigger roles in consortia efforts? Our research suggests several points of resistance:

1. It's complicated. Within drug companies, particularly smaller biotechnology players, specific expertise related to both biomarkers and new trial designs is lacking. This absence, coupled with the execution challenges particular to biomarker and adaptive design adoption, creates an organizational inertia that limits uptake.

Certainly, the state of biomarker science in specific therapeutic areas may complicate a company's precision medicine approach. As MolecularMD's Miller points out, one of the reasons biomarker activity is greatest in oncology stems from the tremendous resources that have been devoted to cancer research since the time of Richard Nixon. "If we'd had a war on cardiovascular disease in addition to a war on cancer," says Miller, "the pool of validated biomarkers would look very different."

Furthermore, translating biomarkers into meaningful tests requires a whole new skill set that diverges from drug development. Companies must choose between different available technologies, being pragmatic about how the testing capabilities may vary in the countries that are considered key target markets.

Similarly, companies that want to run adaptive trials must be able to tap into sophisticated software to ensure they have the ability to manage drug availability and the patient recruitment and randomization process in real time without corrupting the statistical rigor of the study.

We don't deny the complexities associated with either biomarker development or adaptive designs. The available pool of executives who have the expertise to build these programs in-house is small and in high demand. But it is also true that companies do not have to do all of this in-house. Indeed, many smaller companies will choose to partner with other firms, and a growing number of solutions providers have the expertise to run full-fledged precision medicine and adaptive trial programs for companies interested in partnering.

2. It costs too much. While developing a biomarker solution may add up-front costs, this justification is just as likely to be used for avoiding adaptive designs or participation in consortia. Adaptive designs do cost more up front than standard designs, both in terms of additional planning time and capital. But, as we've shown in our analysis, time to market can be shortened dramatically, given that adaptive designs reduce the overall number of patients that must be recruited and eliminate the gap between discrete development phases.

Ultimately, one must measure how the costs of these strategies compare with the cost of a Phase III failure. By lowering scientific risk and allowing the staged investment of capital, biomarkers and adaptive designs play a fundamental role in improving the probability of success and capital allocation associated with drug development. Or, as Graziano Seghezzi, a partner with the Paris-based venture firm Sofinnova Partners, states in the perspective on page 13, the emphasis shouldn't only be on cost-cutting. "The most expensive mistake a biotech company can make when investing resources is to underfund studies and end up with an outcome that falls in a classic gray area: promising, but not definitive. In that case, the company has invested significant financial resources – and time – but still doesn't have much certainty about whether its product is truly differentiated."

Participating in precompetitive consortia also requires the commitment of up-front resources, particularly capital and senior leadership time. Still, this is not a reason not to be involved. As we have pointed out in past issues of *Beyond borders*, companies that join can avoid wasting precious resources on common challenges. Similarly, these initiatives help build trust with other stakeholders – particularly valuable at a time when payers and regulators are bringing more scrutiny to products.

3. Internal incentives get in the way. Based on public comments by senior leaders from big pharma and big biotech, it's clear there is widespread recognition of the utility of precision medicine and precompetitive collaborations in R&D. We've noted smaller biotech companies aren't rushing to participate in precompetitive collaborations in part because of the up-front resource requirement. Misaligned incentives may also play a role, given that the industry's desire to retain control of the data is at odds with academic and nonprofit partners' wish to publish important findings. " It can be very difficult to align these different interests," admits Dr. Michel Goldman of the Innovative Medicines Initiative (IMI). "We believe a third party like IMI has a vital role to play in bringing the different collaborators together."

Current incentive structures may also curb adaptive design usage. Because adaptive designs initially require more up-front resources than traditional studies, companies must adopt what Eli Lilly's Chief Medical Officer, Dr. Tim Garnett, calls a "slow-down-to-speed-up" mentality when devising their programs. That mindset may be at odds with other incentives in small and large companies.

At big biotech and big pharma companies, commercial teams may not be incentivized to support precision medicine approaches if they are measured on overall sales potential of the product. Similarly, R&D teams may be less interested if they are rewarded on the number of assets they advance into later-stage trials rather than on a compound's ultimate performance in the marketplace. In addition, depending on how a company is structured, the individuals that have the greatest familiarity with new trial designs – the biostatisticians – may not have sufficient share of voice to ensure adaptive designs are adopted. Meanwhile, smaller biotech companies may similarly be less interested in adaptive trials if they are cash constrained, in which case "slowing down to speed up" would delay their ability to reach the next value-creating milestone and raise more capital.

While these barriers are real, they are not insurmountable. Large companies can change incentives for R&D teams, as GlaxoSmithKline did in 2013 when it created banker-style bonuses for executives who develop products that make it to market. Clinical program directors, as well as the head of R&D, will likely need to urge more aggressive adoption of both biomarkers and adaptive designs for meaningful change to occur.

Within small firms, CEOs, with the aid of their R&D teams, must have a solid grasp of how adaptive design can enhance the company's capital allocation during development. In particular, R&D teams need to draw a link between abstruse terminology like "covariate adaptive randomization" or "response adaptive randomization" to an improved probability of success and increased estimated NPV. Smaller biotech management teams should also be prepared to clearly communicate to investors the company's expectations related to particular trial designs. That way investors are appropriately able to interpret data released at interim time points, as well as appreciate the capital efficiency benefits expected to be realized from the use of adaptive designs.

4. Standards are poorly defined. When committing to a precision medicine strategy or an adaptive trial design, companies need to understand the associated regulatory requirements. Trouble is, broadly recognized standards outlining the variety and volume of evidence required for either biomarkers or adaptive designs don't yet exist. (Draft sets of guidance on both topics have gone part way to addressing such confusion.) Industry consortia have a key role to play here. On the biomarker front, consortia like the National Biomarker Development Alliance, which formed in early 2014, could play an important role in breaking down and derisking those barriers. When it comes to adaptive trials, precompetitive efforts like IMI's adaptive Alzheimer's disease trials or eXcelerate Research's I-SPY trials reduce confusion by developing validated tools and working with regulators. (For more, see the perspective on page 17 by Meredith Buxton and Peter Payne.)

5. It's hard to do the "killer" experiment. Applying precision medicine and adaptive design to clinical development isn't just about identifying likely winners early in the development cycle. Determining the losers, those products unlikely to meet current efficacy standards, is equally important.

Industry dogma has always been to kill the losers early. Culturally and behaviorally this is hard to do, particularly for smaller companies where a majority of the company's recognized value may be tied to a single asset. Ironically, in attempting to preserve their cherished candidates, leaders may not push for the right experiments early enough in the development cycle because they don't want to uncover potential flaws.

Outside investors must take a more vocal role in advocating for biomarker utilization and adaptive design when appropriate.

This is shortsighted given the growing external pressure to reimburse only for products that are differentiated. Companies may choose to push forward with programs that provide modest improvements in outcomes or safety, but they should understand there is a high risk they won't recoup the dollars invested in such medicines even if they are approved for use in the marketplace. Outside investors are best placed to fight this cognitive dissonance. They must therefore take a more vocal role in advocating for biomarker utilization and adaptive design when appropriate.

Big data in drug R&D

Chris Moore
EY, UK

Partner

Like many other industries, health care is witnessing the emergence of big data, as information streaming in from multiple sources – electronic health records, payer claims, mobile health platforms and more – grows at an exponential rate. This data has the potential to boost the efficiency of drug research and development in three critical ways.

1. Such data helps companies **understand the research landscape**. Today a significant share of research activity is externally sourced from other companies and academic institutions. Consequently, the ability to identify the experts working in particular areas of interest gives a company a competitive advantage in R&D and partnering. Tools such as data mining, automated learning and search can allow companies to pinpoint the important players and get ahead of the competition by buying into promising research early, before it gets phenomenally expensive.
2. Big data also enables drug makers to **decipher a disease's biological derivation or a drug's cause of action**. This might involve identifying a pathway to target or understanding the likely impact of a certain treatment. For instance, the true benefits of chronic disease drugs such as statins take decades to play out. Running a clinical trial to measure these endpoints would be far too lengthy and expensive. Instead, there are platforms that allow companies to use systems biology and crowdsourcing to verify models as well as measure the likely impact of a product over the longer term.
3. Finally, big data can be used to **match the right drugs to the right patient populations**. Data mining and machine learning now allow companies to identify which patient cohorts will be most responsive to specific drugs, using combinations of variables such as gender, ethnicity, disease history and more.

Of course, in today's outcomes-focused environment, such analyses can have a strong financial impact as well. By analyzing how a drug works and in which patients it is most effective, a company can identify additional interventions – including other therapies and delivery mechanisms – that might be needed to boost the product's impact.

Small companies and big data

How can emerging biotechnology companies tap the potential of big data given their resource constraints?

One unfortunate reality is that health care big data is not yet fully democratized, meaning that gaining access remains expensive. A company could easily spend a few million dollars just to obtain the data – a daunting barrier for smaller, resource-constrained firms.

In addition, big data generates insights only when paired with robust analytics. Today, sophisticated algorithms and systems can analyze many more dimensions of data than would have been feasible even a few years ago. However, such processing capabilities are not cheap and are typically beyond the in-house capabilities of smaller companies. And while high-end, cloud-based data analytics are starting to become available, access to such capabilities has not yet filtered down to most smaller players.

As the volume of data grows and more entities create analytics capabilities, gaining access will become easier. Data does not have to come only from commercial organizations looking to sell it for a profit. Disease foundations, government agencies and others are interested in providing data and working with companies that are focused on areas that align with their missions.

Precompetitive collaborations and other consortia can play an important role as well. These joint efforts, typically created to address a shared scientific or methodological challenge, often pool data and devise mechanisms to share it openly with their members. Participating in such efforts gives emerging biotech companies access to data they might not otherwise be able to afford.

Indeed, transforming big data into actionable information is a collective challenge, and one that will require the strengths and capabilities of a diverse set of players. Data held by a consortium may need to be supplemented with analytics capabilities that are starting to become available on a platform basis. Funding for such efforts will typically come from big players. But what might fuse it all together is the creativity and fresh thinking of entrepreneurial, dynamic biotech companies.

Think like a payer

Dr. Silvia Ondategui-Parra
EY, Spain

Partner

We all know decision-making power has shifted to payers and that demonstrating value is a key success factor for life sciences players. Given the ongoing austerity in Europe and rising health care costs elsewhere, biotech companies must step back and reassess their R&D portfolios through the lens of the payer. Do the products under development meet a societal need, as defined and prioritized by specific payers and regulators?

It's a challenging question to answer. As biotech companies assess their portfolios, it raises significant execution challenges. To address these challenges, companies should initiate conversations that seek payer feedback and should ensure they are collecting data that matters to payers.

Seek feedback
Ideally, biotech companies should solicit payer feedback about their products in the earliest stages of R&D, preferably when compounds are preclinical, but especially in Phases I and II. These conversations should take place first at a high level, around therapeutic areas most relevant to payers, and then become more detailed, as specific products are discussed.

Incorporating payer feedback into R&D early on enables firms to optimize and refine their clinical strategies, especially the planned evidence collection. It also allows them to use resources more efficiently. Before companies invest significant money in trials that may not persuade certain regulators or health technology assessment groups, they can get reactions on their proposed designs.

This includes feedback on biomarkers and the use of targeted therapies. Many new molecular tests are very expensive and it's not clear what impact these tests will have on health care budgets. Because the funding model isn't necessarily aligned, payers don't always have the mechanisms to fully leverage biomarkers.

Collect the right data
Biotechs are doing a better job running global, more efficient clinical trials. Still, the types of studies conducted – usually placebo-controlled and randomized – haven't changed much in the last two decades. In particular, companies aren't doing enough to incorporate broader outcomes measures – for instance, data that chart a product's impact on a particular health care system – into their pivotal trials.

Admittedly, collecting these data adds significantly to a trial's costs. Moreover, conducting credible pharmacoeconomic assessments across multiple markets can be difficult. Not only do different payers define unmet need differently, they also use different standards to assess whether that need will be met by a given therapeutic.

One way to address this diversity is through payer segmentation. Another is to develop country-specific data solutions that enable the most efficient spending of public resources. This approach, as we've noted in our pharmaceutical industry report *Progressions 2014: navigating the payer landscape*, requires understanding the individual patient journey in the context of a particular health care system. Then companies can begin collecting the specific evidence required in other health care systems to support the deployment of their products in those markets. The best way to do this is via a well-thought-out project in a market of interest. Companies should work with individual payers in that market to showcase how the product enables better, more efficient care. As the data accumulate, the company can articulate the product's merits to other payers.

Given the current trust deficit between payers and life sciences players, companies will have the most credibility if they forge payer collaborations in conjunction with a neutral third party, whether that's a pan-European organization like the Innovative Medicines Initiative or a country-specific disease advocacy group.

Willingness to partner is necessary but not sufficient. Companies must be flexible in choosing partnership structures that adequately reward all participants.

New capabilities required

It is time for biotech companies, regardless of their size, stage of development or disease focus, to recalibrate their R&D organizations to unlock and capture more value from their drug development efforts. We offer four guiding principles:

1. Partner early — and often. A truly effective precision medicine strategy requires tapping the expertise of an array of stakeholders, many of which are non-traditional partners for biotechnology companies. Organizations such as contract research organizations (CROs), which have played a role in developing companion tests, are moving earlier in the value chain, for instance. Meanwhile, payers, health IT companies and laboratory services companies and diagnostics companies are potential new partners. Companies developing targeted therapies should identify partners that provide the missing skill set required for a successful precision medicine launch. In this way, a biotech company can avoid building out large diagnostics infrastructure, while retaining the flexibility to navigate a quickly changing landscape.

There's no shortage of solutions providers in the adaptive trial space either. In recent years, CROs have devoted significant investment to building the tools and know-how to help optimize clinical designs. Consortia assembled by third parties such as QuantumLeap Healthcare Collaborative and IMI also have expertise and are open to sharing lessons learned.

Willingness to partner is necessary, but not sufficient. Companies must be flexible in choosing partnership structures that adequately reward all participants. In particular, smaller biotech companies looking to access new capabilities should be willing to strike risk-sharing or benefit-sharing agreements with solutions providers to be able to afford their services. Such pacts show there is a shared ethos and that the two parties are in this together. It's worth noting that in the past, certain diagnostic companies struggled because drug developers rejected deal structures that included royalties on product sales. New deal structures are now emerging that allow diagnostic makers to cover their own development costs and reduce reimbursement risk.

2. Empower senior R&D leadership. As we've noted, widespread adoption of precision medicine and new trial designs requires bridging internal cultural divisions. Executives inside and outside the company must commit to asking, both early and often, the question, "Is there a better way to structure this particular development program?"

Given the state of biomarker science and adaptive design, some therapeutic areas will be more appropriate for these tactics than others. R&D teams must be empowered to make those decisions. Senior leadership can help build a culture of appropriate risk-taking by insisting that development groups take a step back and ask some higher-order questions:

- What is the problem we really want to solve? For instance, is it improving probability of success or accelerating development time?
- Is the proposed development approach suited to solve this problem — or should alternates be considered?

As Dr. George Scangos, CEO of Biogen Idec, outlines in the perspective that starts on page 34, "On a daily basis there are seemingly small decisions employees make that have an impact on company performance — and they can make them more conservatively or more aggressively. My goal is to encourage taking risks in the core business of R&D that are reasonable and well thought through where the benefit might be saving time or gaining a new insight."

3. Participate in precompetitive consortia. Precompetitive consortia have a role to play in defining standards and know-how that will broadly benefit life sciences players regardless of their size or disease segment. Because these organizations bring together data streams from diverse sources, they provide an opportunity to connect the dots in a cost-efficient manner. They also enable companies to build trusted relationships with other stakeholders, particularly payers, disease foundations and patients. As we emphasized in the most recent issue of *Progressions*, our sister publication for the pharmaceutical industry, drug companies must overcome a significant trust deficit to be seen as credible partners. One obvious way to build this trust: work alongside other stakeholders to achieve common goals tied to R&D efficiency and the advancement of cures.

4. Prioritize evidence collection initiatives early on. Life sciences companies have always succeeded or failed based on the strength of their data. Increasingly companies will need to develop a coherent strategy for how to use new and different kinds of data amassed during discovery and development to optimize their go-to-market strategies. (For more, see the perspectives by Chris Moore and Dr. Silvia Ondategui-Parra on pages 26 and 27, respectively.)

Companies must prioritize which types of data are most important to collect at the earliest stages of development and then design the trials – whether adaptive or standard – that allow them to most efficiently and credibly collect the information. Such planning is also a requirement for a viable precision medicine strategy. In order to have enough time to validate the drug and accompanying diagnostic simultaneously, biomarker and drug development must run in concert. Too often, companies delay biomarker development until late-stage development, when it is difficult to bring a drug and test to market in parallel and the advantages gained by targeting can no longer be realized.

Adapt and thrive

In his 1945 work, *The Mind at the End of its Tether*, H.G. Wells famously wrote that "nature's inexorable imperative" is to "adapt or perish." This is an imperative that biotechnology companies, which have survived ebbs in funding and investor sentiment, have long lived by.

Never has biotech's agility been more important than now, as the current challenges facing the industry are more persistent and consequential than in decades past. Two seismic shifts underpin the need to unlock value. The first of these, a resource-constrained environment for R&D – the recent US IPO window notwithstanding – is here to stay. The second big shift – the move by health care systems toward outcomes and value – means drugs inevitably face more scrutiny, not just from payers but also from financial and strategic investors.

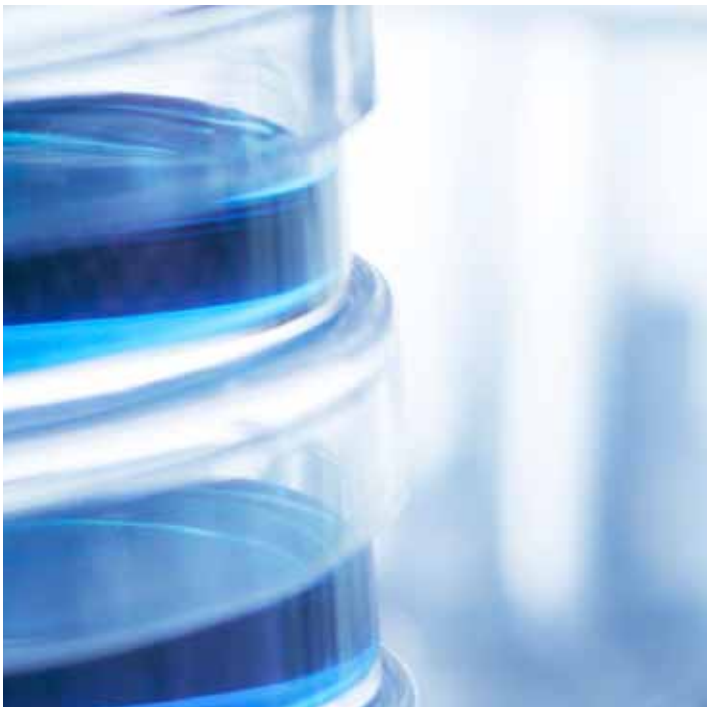
Never has biotech's agility been more important than now, as the current challenges facing the industry are more persistent and consequential than in decades past.

These pressures make approaches such as precision medicine and adaptive trials all the more relevant for differentiating products and capturing value. And, at a time when it is critical for companies of all sizes to conduct R&D in capital-efficient ways – most small companies face capital constraints and many large ones have relatively little to show for their R&D expenditures – adaptive trials, biomarkers and precompetitive collaborations provide ways to deploy resources judiciously.

If use of these strategies is to expand, underlying challenges will need to be addressed. As we've discussed, increasing R&D efficiency will require embracing new kinds of partners and partnership models to access needed capabilities and solve logistical complexities. It may mean thinking slow and small at the outset of development in order to gain speed and market acceptance at the other end.

Recalibrating R&D to take advantage of these scientific and statistical advances will require changes from other stakeholders too. Regulators around the globe will need to adapt their frameworks to enable drug development paradigms that are flexible and learn in real time. Payers and governments will need to find ways to work with drug companies to ensure industry can continue to afford to invest in the collection of evidence that matters to patients and caregivers.

We believe this industry is well prepared to adapt to the evolving market realities. Health care's move to value is, in part, driving biotech's need to unlock value. Getting there will require the sector to tap into its long-standing *values* – its foundation in data-driven approaches, willingness to partner creatively and, ultimately, its adaptability in the face of new challenges.



New expedited regulatory pathways speed products to market

Rachel King
GlycoMimetics

CEO and
Biotechnology Industry
Organization Chairwoman

As CEO of a pre-commercial biotech company that recently completed an initial public offering, I am well aware that despite the recent IPO window, we continue to live in a capital-constrained environment. Companies that feel flush with cash must continue to be focused and wise stewards of their resources. Yet we must also acknowledge that the regulatory environment can influence the investment climate. In order to continue to bring innovative medicines to market, we must promote forward-thinking regulatory policies that help speed new cures to patients.

In our current environment, the availability of multiple expedited approval pathways – including the new Breakthrough Therapy Designation program the U.S. Food and Drug Administration (FDA) created under the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) – is an important and positive development. On 29 May 2014, the FDA released its final guidance on expedited development programs for serious conditions. (See the table at right.)

Even before the release of this document, however, the expansion of approval pathway options has had a material impact on therapeutic development. Thus far, drug sponsors have made 189 requests for the breakthrough designation, 50 of which have been granted. Indeed, more than half of the novel drugs the FDA's Center for Drug Evaluation and Research (CDER) division approved in 2013 used some combination of those tools to speed promising therapies to patients with serious conditions.

Admittedly, companies continue to work with regulators to understand implementation issues tied to the various expedited pathways. For instance, in its final guidance, the FDA clarified how intermediate clinical and surrogate endpoints can serve as a basis for accelerated approval but fell short of providing a definitive framework for their appropriate use. In theory, the May 29 document better defines when a therapy is considered a breakthrough; in practice there is likely to be continued confusion about what kinds of data – and how much – are required to support given regulatory designations.

The lack of clarity adds some uncertainty. But it is a reality drug sponsors must live with if they want to retain the right to request a specific expedited pathway rather than have the regulators solely responsible for the determination. More importantly, these pathways formally give the FDA flexibility to work with a sponsor to speed the launch of novel products needed and wanted by patients. You see that flexibility in the FDA's stance on accelerating the approval of much-needed antibiotics. At a time when innovative products are under pressure elsewhere, this flexibility is really encouraging.

The breakthrough therapy designation is important because it enables deeper and more frequent discussions with regulators during the development process for products that show preliminary evidence of providing substantial improvement over existing treatments. Regulators have promised an "all hands on deck" mentality. This includes a willingness to engage with drug developers as needed on the most relevant ways to develop products, from the selection of surrogate endpoints to nuances related to different trial designs. These enhanced communications are critical since these products treat unmet needs for which there are no approved drugs.

At GlycoMimetics, we are enthusiastic about the potential opportunities new expedited pathways create for our pipeline products. As an industry, we must work together to ensure the FDA has the scientific capacity, resources and statutory flexibility necessary to continue to efficiently evaluate novel medical treatments. We must also recognize the direct link between the regulatory flexibility embodied in the FDA's expedited programs and the positive investment climate they promote. This creates a virtuous cycle fueling future innovation, which ultimately benefits the patients we all serve.

FDA's expedited drug review programs

Program (enacting legislation)	Submission and FDA response timelines	Criteria for eligibility	Key points to consider
Fast Track designation (Section 506(b) of the FD&C Act, amended by section 901 of FDASIA 2012)	• Request ideally submitted with IND; should be submitted no later than pre-BLA or pre-NDA meeting • FDA will respond within 60 calendar days of receipt of request	Treats a serious condition and non-clinical or clinical data demonstrate the potential to address an unmet medical need; or product is qualified infectious disease product	• Does not guarantee breakthrough designation • Is not correlated with Priority Review • May or may not utilize surrogate endpoints • Drugs denied Breakthrough Therapy designation may reapply for Fast Track designation • Potential for expedited or rolling review • Designation can be rescinded if it no longer meets qualifying criteria for Fast Track
Breakthrough Therapy designation (created by FDASIA 2012)	• Request submitted with IND or after, ideally no later than the end-of-Phase II meeting • FDA will respond within 60 calendar days of receipt of request	Treats a serious condition *and* preliminary clinical data exist showing drug demonstrates a substantial improvement on a clinically significant endpoint over current therapies	• Higher level of evidence required than for Fast Track designation • All drugs with Breakthrough Therapy designation also have Fast Track designation. • Provides more frequent communications with top FDA staff • Associated with faster approval process but not necessarily given Priority Review designation; rolling review • Can be rescinded if data emerge showing no better than current standard of care
Accelerated Approval (Section 506(c) of FD&C Act, amended by FDASIA 2012)	• Pathway use determined during drug development in conjunction with FDA review division • No specified time for regulatory response	Treats a serious condition *and* provides meaningful advantage over existing therapies *and* this advantage can be demonstrated via a surrogate marker	• Approval is based on an intermediate clinical endpoint or surrogate endpoint that predicts medical benefit • New 2014 draft guidance suggests accelerated approval status will be clearly stated in the drug label • Continued approval may be contingent upon demonstration of clinical benefit • Approval is subject to expedited withdrawal if the product does not demonstrate efficacy in a post-marketing study
Priority Review (PDUFA 1992)	• No separate submission required; FDA assesses each BLA or NDA for priority review • FDA will respond within 60 calendar days of receipt of BLA, NDA or efficacy supplement	An application for a drug that treats a serious condition; if approved, this product provides a meaningful improvement in clinical benefit or safety	• Shorter clock for review of marketing application: 6 months versus 10-month standard • Priority Review status determined separately from Fast Track or Breakthrough Therapy designation • Drugs submitted with Priority Review vouchers qualify for this pathway

Source: "Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics," FDA May 2014, p. 11-12.

Improving biopharma innovation: collaboration required

Dr. Elias Zerhouni
Sanofi

President, Global R&D

The future of biopharma innovation requires collaboration: companies need to collaborate not just with each other but with academics, public and private payers, providers, not-for-profit organizations and, of course, patients. We must work together, precompetitively sharing biomarker, clinical and epidemiological data to further the industry's understanding of human disease. In addition, we must collaborate to harmonize the diverse regulatory practices that exist around the globe. If we do not find new ways to work together, our ability to bring innovative new medicines to market remains at risk.

We all know biopharmaceutical R&D productivity has dropped significantly. In spite of remarkable scientific progress and an explosion in potential new drug targets, our capacity to translate advances such as the sequencing of the human genome into effective health benefits has decreased.

Part of the problem is that our current paradigm treats every disease as an acute condition that can be explained by primary, unchanging drivers that remain constant over the course of the disorder. That's a very 19th-century way of looking at disease that doesn't take full advantage of 21st-century capabilities. We know, for instance, that what we label multiple sclerosis is actually a cluster of biological events that include autoimmune triggers in the earliest stages of the disease and progressive neurodegeneration at the later stages. Is it logical to treat early- and late-stage multiple sclerosis exactly the same way given that the underlying biological defects could be very different as the disease evolves?

Obviously not.

But our current understanding of how to intervene in chronic diseases, such as MS, Type 2 diabetes or even cancer, is constrained by our vertically siloed research model, in which findings are sequentially moved from the laboratory to the clinic to the real world. Thus, knowledge gleaned at the point of care isn't easily or rapidly shared with R&D teams to influence drug development. Moreover, learnings attained in one disease area don't necessarily spread to other therapeutic areas. This is the real translational divide limiting biopharmaceutical innovation.

Bridging this divide requires a networked approach in which different stakeholders broadly and prospectively collect and share different kinds of data with each other. At each step in the drug development continuum, new kinds of collaborations could help solve specific problems that broadly hurt the health care ecosystem. For instance, in early research, we need to move away from our reliance on surrogate markers and confirm disease using biomarkers and cell lines that are predictive. Efforts to build libraries of validated biomarkers and screening tools require the collective effort of companies, academia and governments. Both the Innovative Medicine Initiative in Europe and the US's National Institutes of Health have played a vital role in spearheading investment in this arena.

As products move into the clinic, industry must collaborate with clinical investigators and regulators to develop novel methods of predictive safety, embracing new biostatistical approaches and adaptive trial designs in the process. Researchers across the ecosystem must also join forces to identify new mechanisms that better define chronic diseases by their underlying etiologies.

When products come to market there is a real need for dynamic registries to collect data and personalize treatment guidelines. Currently there are five different TNF-alpha inhibitors on the market to treat rheumatoid arthritis; patients cycle through these therapies based on trial and error. We need to do a better job of understanding which patients respond to particular therapies so that we can target *a priori* specific medicines to specific patients. Creating and maintaining such registries requires the collaboration of industry with payers, physician groups and patient advocacy organizations. Until we can reduce the prescribing of ineffective therapies, health care dollars will be wasted. More importantly, we waste patients' time.

Finally, payers, health systems, providers and industry must also join forces to ensure effective medicines are utilized in a way that truly modifies the disease process in the population at large. Such "implementation research" must measure how new delivery tools (e.g., disease management programs or novel drug delivery systems) affect patients' health outcomes.

Of course, collaborations of this scale, which span the R&D continuum, will generate staggering amounts of data. This, in turn, will necessitate data analytics capabilities beyond those of any one company, any one institution or any one country. The data explosion also requires that large companies rethink how we work with smaller biotech players. As we move from a siloed, inward-oriented R&D model to one that is networked, we need to embrace longitudinal partnership models both financially and operationally. We should forge relationships with early-stage biotech companies and academic centers that aren't event-based but are long-lasting and enable the collection of different types of data.

Solving the regulatory divergence problem

Even as we rethink how we interact with other stakeholders to bridge the current translational divide, we also need to solve what I call the regulatory divergence problem. We have reached the point where regulatory complexity around the globe is creating meaningful barriers to product innovation.

The world is certainly globalizing; at the same time, however, regulatory agencies are diverging. Each country has different rules and requirements that collectively make the whole system less effective and wasteful. At Sanofi, we now spend an enormous amount – probably 20% of our development budget – trying to manage disparate regulations. The industry needs an international contract to oversee the regulation of medicines, akin to the international commerce treaty governing monetary exchange or the global aviation standards that regulate air travel and safety.

Can you imagine what it would be like if the suboptimal system we use to manage food and drugs were applied to air travel? Every time you crossed the border into a new country, you would need to land the plane and change its design before you could proceed. It would be chaos; we wouldn't travel.

Given the trans-border nature of developing medicines, I believe the G7 or G20 countries must come together to define international standards for food and drug safety. I'm not saying that standards shouldn't be rigorous – just that they should be harmonized. For this to occur, regulatory science needs to improve and we must move past confrontational issues that have pitted the FDA against the European Medicines Agency. When there's a regulatory question, countries must work together to find a common solution instead of each group devising its own approach.

This lack of regulatory harmony isn't a company issue. It's a health advocacy issue leading to an enormous waste of opportunity, talent and money. We owe it to patients to stand up and call for international regulatory standards.

Preserving a culture of innovation

Dr. George Scangos
Biogen Idec

CEO

As biotech companies grow into commercial enterprises, they invariably confront a common challenge: how to preserve their innovative cultures without falling victim to the bureaucracy that often hampers big companies. A company's culture is influenced by its structure and incentives; at Biogen Idec, we have adopted approaches for both aspects that might be useful for other growing firms.

Structuring R&D

While innovation occurs everywhere in our organization, our mission demands that, ultimately, it comes from research and development. And while development scales well, research does not. As a result, we have structured R&D to reflect the unique challenges at both ends of the process.

In research, we focus on building a team of world-class scientists and collaborating with top university researchers. It takes time and money to validate putative drug targets, so companies typically do this work in series. We have developed methods – using both internal technologies and external collaboration – to test targets in parallel, allowing us to move more quickly from an untested hypothesis to a legitimate target.

To accelerate the transition from the laboratory to the clinic, we have formed smaller groups that work on specific areas, for instance value-based medicine and "iHubs" focused on specific diseases. These groups span the bridge between discovery and early development. Their mission is to understand drug mechanisms, get some proof-of-concept data and then move compounds rapidly into clinical trials.

Our development teams are structured in ways that allow us to benefit from the scale of a large organization while preserving the flexibility and innovation of a start-up. One leader is in charge of each drug project, from early development through marketing. This individual – a "mini-CEO" for that drug – is supported by a team of people from different departments, including R&D, marketing, technical operations and legal. Decisions about individual projects are made by project teams, while prioritization decisions across projects are made at the management level.

Indeed, decision-making clarity is a critical component in preserving a culture of innovation. Empowering leaders doesn't mean just giving them a blank check. It means identifying clearly which decisions managers have the authority to make – and not second-guessing those decisions once they are made.

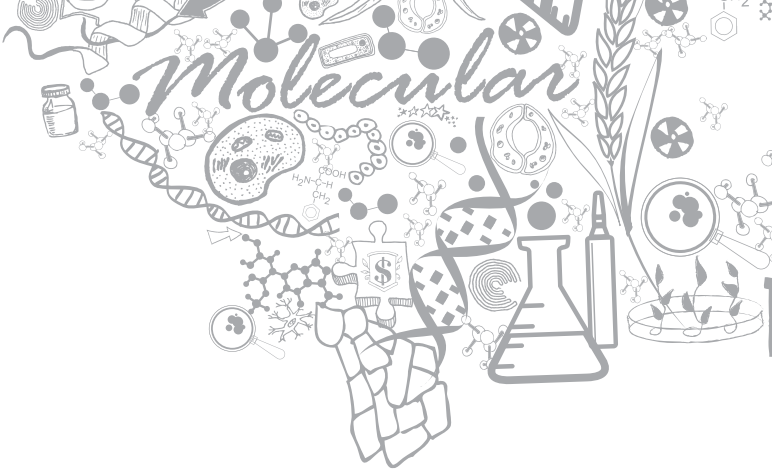
For instance, in our organization, decisions about Phase III trials – which are big, expensive and consume a lot of resources – are made at a higher level, while decisions about smaller investments are made by project teams.

This structure allows us to emulate an ecosystem of emerging companies within a larger entity. Each project team brings the passion and innovative spirit of a start-up. At the same time, the larger organization brings resources and discipline that true start-ups often lack.

Creating incentives

Preserving a culture of innovation also requires the right incentives. On a daily basis, there are seemingly small decisions employees make that have an impact on company performance – and they can make them more conservatively or more aggressively. My goal is to encourage taking risks in the core business of R&D that are reasonable and well thought through, where the benefit might be saving time or gaining a new insight. This requires that we reward, rather than punish, failure that stems from appropriate risk-taking.

To encourage behaviors that are vital for innovation, such as risk-taking, collaboration and sharing, we have restructured our annual review and compensation system. Half of employees' performance scores are based on their accomplishments – did they reach their goals? But the other half is based not just on what they did, but on how they did it – did they team well, take appropriate risks, did they collaborate with other parts of the organization, and did they behave in ways consistent with our values?



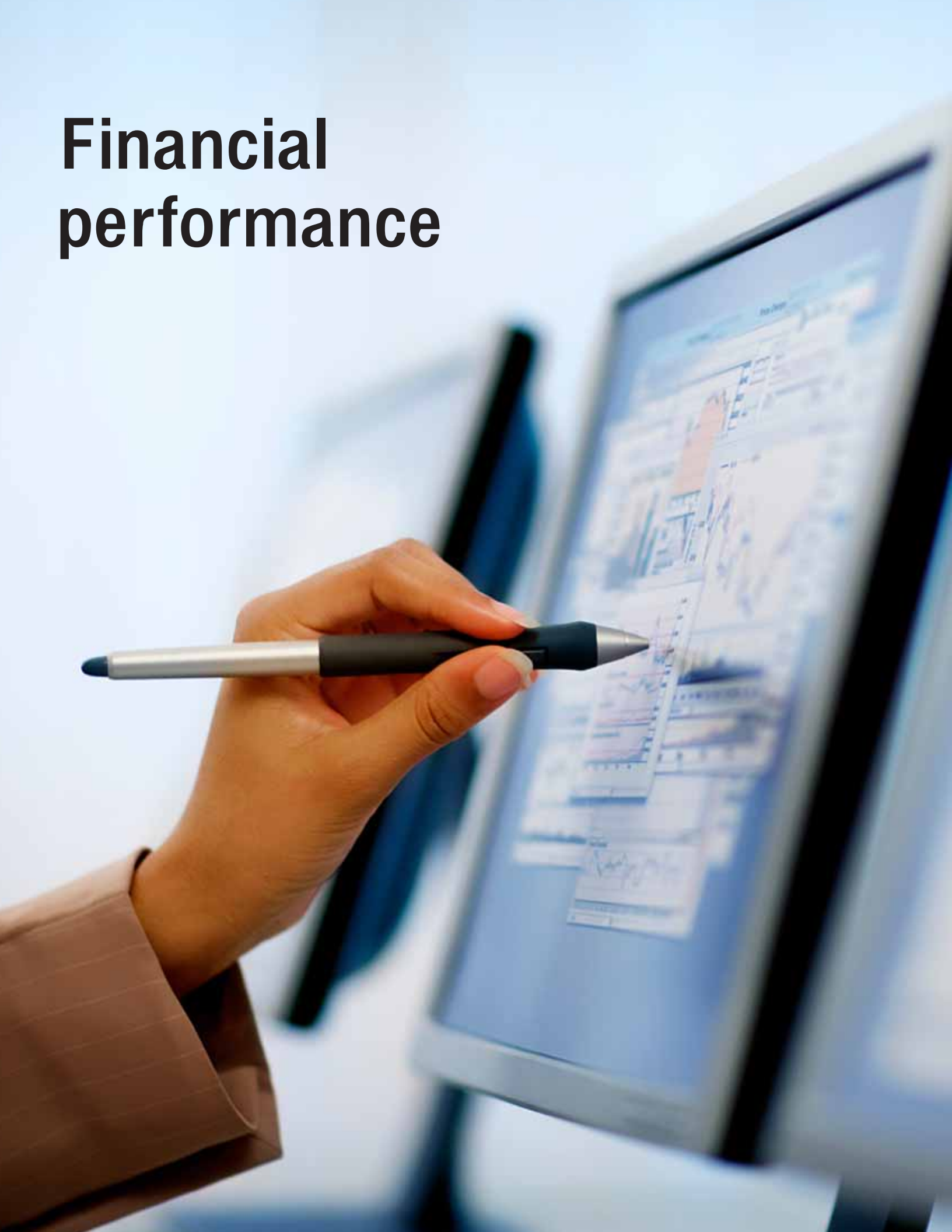
Looking ahead

As we grow, the challenge of preserving an innovative culture will become even more pronounced. So far, all of our R&D is in one location in Cambridge, Massachusetts. The team is small enough that it's still possible to know most of the people.

Growth will require the company to become more complex. Our systems and the way people do their jobs will have to change. When you have one or two products, the head of every department can be involved in every decision about those products. When you have six products, they can't. Processes that were performed manually will have to be automated. People who used to manage processes will have to learn to manage people who are managing processes – and do so without creating lots of bureaucracy or micromanaging.

I believe that successfully navigating such transitions will require the same overall principle that has guided our efforts so far: creating structures and incentives that allow us to preserve the nimbleness and innovation of start-ups while benefiting from the scale and rigor of a larger company.

Financial performance



Commercial leaders

The big picture

The performance of the biotechnology industry was strong in 2013, with revenues of publicly traded companies in the four established centers of the US, Europe, Canada and Australia increasing by a robust 10% relative to 2012. However, this performance varied significantly by geography and company size. In particular, as discussed below, the strong product launches and financial results of a relatively small number of US-headquartered "commercial leaders" (a group we define to include companies with revenues in excess of US$ 500 million) drove the majority of the industry's gains.

In an encouraging development, R&D spending rebounded forcefully to return to historic levels for the first time since the start of the global financial crisis. While growth in R&D spending in this research-driven industry has traditionally kept pace with top-line growth, this trend was reversed in the aftermath of the financial crisis. In 2008, R&D spending *declined* for the first time in the industry's history, as companies slashed spending in a severely resource-constrained environment. Over the next few years, even as R&D growth inched back into the black, it continued to trail growth in revenues. In 2013, that pattern was finally broken, as the industry grew R&D spending by a very healthy 14% – four percentage points higher than growth in the top line. However, the story is not the same everywhere. While R&D spending was up 20% in the US, it actually dropped 4% in Europe, indicative of a much more constrained financing environment and an industry that experienced lower overall revenue growth.

The industry's net income declined by US$ 0.8 billion, driven in part by the US$ 3.7 billion increase in R&D expenditures. As discussed in prior issues of *Beyond borders*, the industry had not been profitable in the aggregate before the global financial crisis, when profitability became a byproduct of across the board spending cuts. The 2013 net income story also varied by geography – net income skyrocketed in Europe even as it declined in the US. To the extent that increasing R&D expenses eroded earnings growth at the commercial leaders, however, that only reinforces a point we make in this year's "Point of view" article: biotech companies need, more than ever, to conduct R&D in the most capital-efficient manner possible. (For more on this, see the "Point of view" article on page 7.)

Growth in established biotechnology centers, 2012–13 (US$ b)

	2013	2012	% change
Public company data			
Revenues	98.8	89.7	10%
R&D expense	29.1	25.4	14%
Net income	4.3	5.1	-15%
Market capitalization	791.8	478.7	65%
Number of employees	178,850	165,400	8%
Number of companies			
Public companies	616	602	2%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

The number of public companies increased by 2%, driven by the addition of 49 IPOs in the US and Europe, as well as the removal of a number of companies from the roster through acquisition, de-listing or other developments. The US total grew by 23, while Canada lost six, Australia two and Europe one.

EY survival index, 2012–13

	US		Europe		Canada	
	2013	2012	2013	2012	2013	2012
More than 5 years of cash	27%	22%	33%	33%	24%	16%
3-5 years of cash	16%	9%	8%	5%	7%	3%
2-3 years of cash	11%	16%	10%	12%	5%	8%
1-2 years of cash	23%	21%	16%	16%	5%	18%
Less than 1 year of cash	23%	33%	33%	34%	59%	54%

Source: EY and company financial statement data.
Chart shows percentage of biotech companies with each level of cash. Numbers may appear inconsistent because of rounding.

Commercial leaders and investor confidence

The accomplishments of a few commercial companies helped shape the industry's strong performance and boost investor sentiment toward the sector. Virtually all of the global industry's 2013 revenue growth came from the 17 US-based commercial leaders, which posted strong increases in revenue and profits on the back of important new drug launches. The market rewarded the performance of these companies by pushing their market capitalizations up a remarkable US$ 201.9 billion. And, in a case of a rising tide lifting all boats, that outsized performance – which actually began in 2012 – increased enthusiasm in the sector overall and helped bring back generalist investors seeking returns, which in turn helped to catalyze the strong IPO market.

Among the commercial leaders, three companies – Biogen Idec, Celgene and Gilead Sciences – were the biggest drivers of growth. Celgene's market cap grew 110% to US$ 69.6 billion, Biogen Idec's by 91% to US$ 66 billion, and Gilead Sciences' by 107% to US$ 115.2 billion, taking it past Amgen to become the world's highest-valued biotech company.

The amount of capital made available by investors, particularly to earlier-stage companies, helped fuel the rebound in R&D spending. Many companies were able to "refill their tanks" in 2013 through IPO or follow-on offering transactions (for more, see "Financing" section on page 53). The four biggest biotech companies by market cap in 2013 – Gilead Sciences, Amgen, Celgene and Biogen Idec – were also the biggest investors in R&D for the year, between them spending almost US$ 9.9 billion (the remaining 335 US publicly listed biotechs spent US$ 13.4 billion).

US companies with largest increases in market capitalization, 2012-13 (US$ b)

Company	Market cap 2013	Market cap 2012	US$ change	% change
Gilead Sciences	115.2	55.6	59.5	107%
Celgene	69.6	33.2	36.4	110%
Biogen Idec	66.0	34.6	31.4	91%
Amgen	86.0	66.1	19.9	30%
Regeneron Pharmaceuticals	26.8	15.9	10.9	69%
Vertex Pharmaceuticals	17.4	9.1	8.3	91%
Alexion Pharmaceuticals	26.1	18.2	7.8	43%
Illumina	14.0	6.9	7.1	104%
Incyte Corporation	8.2	2.2	6.0	274%
Life Technologies	13.1	8.4	4.7	55%
BioMarin Pharmaceutical	10.0	6.1	3.9	64%
Pharmacyclics	7.8	4.0	3.8	94%
ISIS Pharmaceuticals	4.6	1.1	3.6	338%
Salix Pharmaceuticals	5.7	2.4	3.3	138%
Alnylam Pharmaceuticals	4.1	1.0	3.1	326%
United Therapeutics	5.7	2.7	3.0	109%
Puma Biotechnology	3.0	0.5	2.4	453%
Cubist Pharmaceuticals	5.1	2.7	2.4	88%
NPS Pharmaceuticals	3.1	0.8	2.3	293%
Seattle Genetics	4.9	2.8	2.1	77%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

United States

In 2013, the US biotech industry's revenue growth rebounded to 13% – the best showing since the start of the global financial crisis and a marked improvement over the 8% growth in 2012. A full percentage point of this increase came from the IPO class of 2013, which collectively added US$ 662 million to the industry's revenues.

Driven by strong product launches and sales growth, three stalwarts – Amgen, Biogen Idec and Gilead Sciences – delivered the biggest increases in revenues, of more than US$ 1.4 billion each. Vertex Pharmaceuticals experienced the biggest drop in revenues, down by US$ 315 million after new competition drove down sales of its hepatitis C drug, Incivek, from US$ 1.16 billion in 2012 to US$ 466 million in 2013. However, the company filled some of the gap with increased revenues from its cystic fibrosis drug, Kalydeco, which jumped from US$ 171.6 million in 2012 to US$ 371.3 million in 2013, largely through European sales. At the end of the first quarter of 2014, Vertex announced that it would quit its hepatitis C R&D program to focus on cystic fibrosis.

Strong revenue and product stories helped fuel a dramatic increase in market capitalization, which was up 75% in 2013, on top of 30% growth in 2012. Three-quarters of companies, 220 in all, grew their market caps, 46 of them by over 250% and 102 by more than 100%.

US biotech companies responded enthusiastically to their top-line growth and a more robust equity market by increasing their R&D spending by 20% relative to 2012, up from 2012's mere 7% increase over 2011. Nearly 60% of companies (247 of 339) increased their R&D spending in 2013, and 116 decreased it. Commercial leaders increased R&D spending by 25%, including Cubist (a 73% increase), United Therapeutics (72%) and Celgene (39%).

Net income declined by US$ 1.8 billion in 2013 – a 42% drop from 2012 that resulted from increased R&D spending and, to a lesser extent, declining sales at some companies. Only 43% of the 339 public biotech companies in the US recorded a positive bottom line (although Amgen's was an outsized US$ 5.1 billion), and 176 recorded a drop in net income (or an increase in net loss) year-on-year.

Along with reinvestment in R&D, many US biotech companies boosted headcount in 2013. Employee numbers were up 10% in 2013, after growth of just 2% in 2012. Three-quarters of companies either grew in headcount or at least kept their payrolls at 2012 levels.

US biotechnology at a glance, 2012–13 (US$ b)

	2013	2012	% change
Public company data			
Revenues	71.9	63.7	13%
R&D expense	23.3	19.4	20%
Net income	2.6	4.4	-42%
Market capitalization	633.0	361.3	75%
Number of employees	109,530	99,910	10%
Financing			
Capital raised by public companies	19.7	18.9	4%
Number of IPOs	41	12	242%
Capital raised by private companies	5.6	4.8	17%
Number of companies			
Public companies	339	316	7%
Private companies	2,010	2,061	-2%
Public and private companies	2,349	2,377	-1%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

In any year, growth rates are driven not just by organic growth at existing companies, but also by significant changes to the company list. In prior years, for instance, we have often had to normalize the numbers to account for the skewing effect of megamergers that removed large biotech companies from the list. In 2013, the numbers were not distorted by any such huge transactions – the largest biotech company taken out, Onyx Pharmaceuticals, only had revenues of about US$ 360 million in 2012. What *was* unusual in 2013 was the large volume of IPOs. Because of the sheer number of new listings, these companies collectively had a palpable impact on the industry's overall performance. That's because the typical IPO company is very different from the traditional commercial leader (for instance, new IPOs have lower revenues and higher net losses). Normalizing for the year's IPOs, the industry's revenue growth would have been 12% instead of 13%. Market cap would have increased by 70% instead of 75%. R&D growth would have been 14% instead of 20% – encouragingly, still outpacing top-line growth, but by a much narrower margin. Most significantly, the industry's net income would not have declined by 42%, but rather by 16%. As already discussed, much of this 16% decline was due to the increased spending on R&D, with the remainder driven, as it is in any year, by one-time events and increases in SG&A expense at specific companies.

US commercial leaders, 2009-13

2009 13 companies	2010 16 companies	2011 16 companies	2012 16 companies	2013 17 companies
Organic growth →	Alexion	Alexion	Alexion	Alexion
Amgen	Amgen	Amgen	Amgen	Amgen
Amylin	Amylin	Amylin	Acquired by BMS	
Biogen Idec	Biogen Idec	Biogen Idec	Biogen Idec	Biogen Idec
		Organic growth →	Biomarin Pharmaceutical	Biomarin Pharmaceutical
Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories	Bio-Rad Laboratories
Celgene	Celgene	Celgene	Celgene	Celgene
Cephalon	Cephalon	Acquired by Teva		
Cubist	Cubist	Cubist	Cubist	Cubist
Organic growth →	Gen-Probe	Gen-Probe	Acquired by Hologic	
Genentech	Genentech	Acquired by Roche		
Genzyme	Genzyme	Acquired by Sanofi		
Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences	Gilead Sciences
IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories	IDEXX Laboratories
Illumina	Illumina	Illumina	Illumina	Illumina
Life Technologies	Life Technologies	Life Technologies	Life Technologies	Life Technologies
			Organic growth →	Myriad Genetics
		Organic growth →	Regeneron Pharmaceuticals	Regeneron Pharmaceuticals
	Organic growth →	Salix Pharmaceuticals	Salix Pharmaceuticals	Salix Pharmaceuticals
Talecris Biotherapeutics	Talecris Biotherapeutics	Acquired by Sanofi		
		Organic growth →	The Medicines Company	The Medicines Company
Organic growth →	United Therapeutics	United Therapeutics	United Therapeutics	United Therapeutics
	Organic growth →	Vertex Pharmaceuticals	Vertex Pharmaceuticals	Vertex Pharmaceuticals
	Organic growth →	ViroPharma	Decline in sales	

Source: EY, Capital IQ and company financial statement data.
Commercial leaders are companies with revenues in excess of US$ 500 million.

The 16 US commercial leaders of 2012 were joined by a new arrival, Myriad Genetics, and for the first time since 2010, no commercial leader was removed from the list by acquisition. Nearly 75% of the US biotech sector's total 2013 revenue growth came from just five of these companies (Gilead Sciences, Biogen Idec, Amgen, Celgene and Regeneron Pharmaceuticals) boosted by new product launches (such as Biogen Idec's Tecfidera, which brought in US$ 876 million) and continued strong performance in key disease franchises. Gilead Sciences passed the US$ 10 billion revenue mark, reaching US$ 11.2 billion, although it still has a way to go to catch perennial leader Amgen, with its US$ 18.7 billion.

US biotechnology: commercial leaders and other companies, 2012–13 (US$ b)

	2013	2012	US$ change	% change
Commercial leaders				
Revenues	61.8	54.0	7.9	15%
R&D expense	14.4	11.5	2.9	25%
Net income (loss)	12.9	12.1	0.8	7%
Market capitalization	473.3	271.3	201.9	74%
Number of employees	76,185	67,610	8,575	13%
Other companies				
Revenues	10.1	9.8	0.3	3%
R&D expense	8.9	8.0	1.0	12%
Net income (loss)	(10.3)	(7.6)	(2.7)	35%
Market capitalization	159.8	90.0	69.7	77%
Number of employees	33,367	32,329	1,038	3%

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

The skewed nature of the US biotechnology market is starkly visible in this analysis of commercial leaders compared to the rest of the industry. The 17 largest US companies accounted for US$ 7.9 billion of the US$ 8.2 billion increase in revenues. The other 322 companies accounted for the remaining 4% of revenue growth.

It was encouraging, if perhaps somewhat unsurprising, that the distribution of R&D spending was not as skewed, with commercial leaders accounting for about 75% of R&D expenditures. The rest of the industry grew R&D spending by 12% relative to 2012 – about half the percentage increase at the commercial leaders, but still a robust double-digit increase that kept pace with the overall top-line growth of the US industry.

The divide between the two segments was starkest when it came to profitability. While the net income of commercial leaders rose 7%, the rest of the industry went 35% deeper into the red as a result of increased R&D spending and the addition of the IPO class of 2013. The rise in R&D spending suggests a rising confidence in the availability of capital to fund drug development.

The capital markets' improved sentiment toward biotech did not, however, discriminate between large and small companies. If anything, the percent increase in market capitalization was slightly higher for non-commercial leaders (77% compared to 74%). This was due in part to the large number of IPOs; but even after normalizing for the IPO class of 2013, non-commercial leaders experienced an impressive increase in market cap of about 56%.

The IPO class of 2013 also had an impact on other variables. Without the year's IPOs, non-commercial leaders' revenues would have declined by 4% instead of increasing by 3%. R&D expense would have declined by 2% instead of increasing by 12%. And net loss would have increased by 19% instead of 35%.

Selected US biotechnology public company financial highlights by geographic area, 2013
(US$ m, % change over 2012)

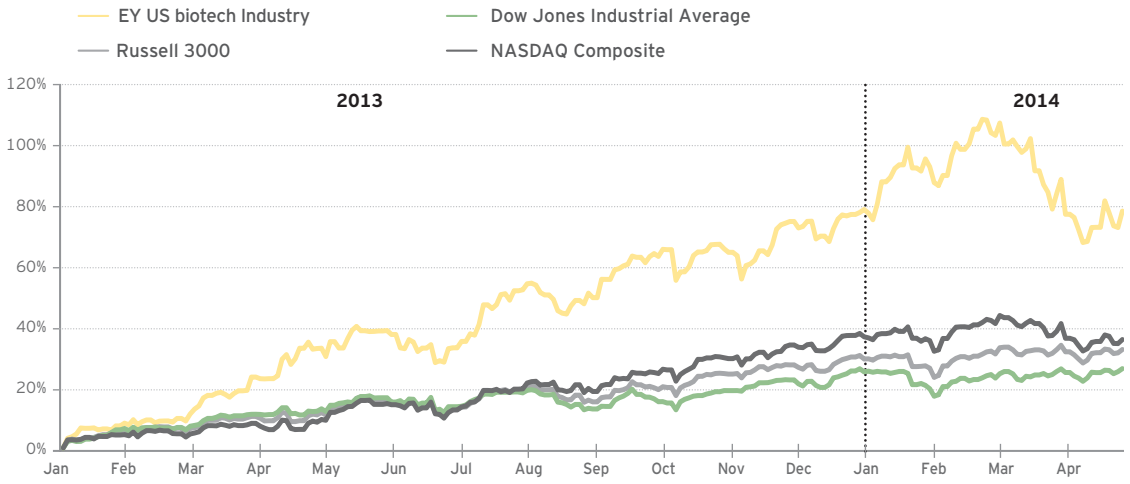
Region	Number of public companies	Market capitalization 31 Dec 13	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term investments	Total assets
San Francisco Bay Area	66 2%	170,478 78%	16,777 11%	5,081 8%	214 -833%	10,493 -2%	37,463 8%
New England	58 18%	148,008 71%	12,993 15%	5,253 25%	(638) -289%	9,517 -14%	27,133 23%
San Diego	38 9%	45,949 88%	6,117 7%	1,546 17%	(471) 45%	4,149 2%	14,987 7%
New York State	29 0%	34,208 73%	2,831 36%	1,224 23%	(104) -115%	1,911 42%	4,982 41%
New Jersey	22 10%	79,572 116%	7,506 19%	2,712 23%	1,086 -2%	6,494 23%	14,450 7%
Mid-Atlantic	19 12%	13,511 161%	1,723 16%	739 36%	(87) -243%	1,588 32%	3,983 33%
Southeast	17 -6%	5,310 102%	266 19%	202 7%	(346) 58%	499 33%	1,824 157%
Los Angeles/Orange County	15 7%	92,802 36%	18,972 9%	4,375 19%	4,578 16%	19,967 -56%	67,959 24%
Pacific Northwest	12 0%	7,111 66%	660 16%	530 27%	(694) -5%	862 -34%	1,350 -7%
Pennsylvania/Delaware Valley	11 0%	13,512 178%	1,194 5%	504 25%	(396) 465%	552 -26%	1,451 8%
Midwest	11 10%	2,637 86%	111 155%	197 -15%	(427) 24%	446 11%	717 26%
North Carolina	11 22%	7,990 158%	972 13%	369 30%	(149) 159%	1,715 37%	3,545 50%
Texas	8 0%	2,435 9%	260 19%	174 13%	(107) -24%	222 -39%	462 19%
Colorado	6 0%	3,008 197%	70 -18%	151 19%	(184) 53%	149 -43%	191 27%
Utah	4 33%	2,015 -13%	613 24%	61 5%	122 55%	422 -2%	856 9%
Other	12 20%	4,428 66%	848 11%	167 44%	170 -31%	595 -15%	1,636 38%
Total	**339** **7%**	**632,975** **75%**	**71,912** **13%**	**23,285** **20%**	**2,566** **-42%**	**59,581** **-30%**	**182,991** **18%**

Source: EY and company financial statement data.
Percent changes refer to change over 31 December 2012. 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

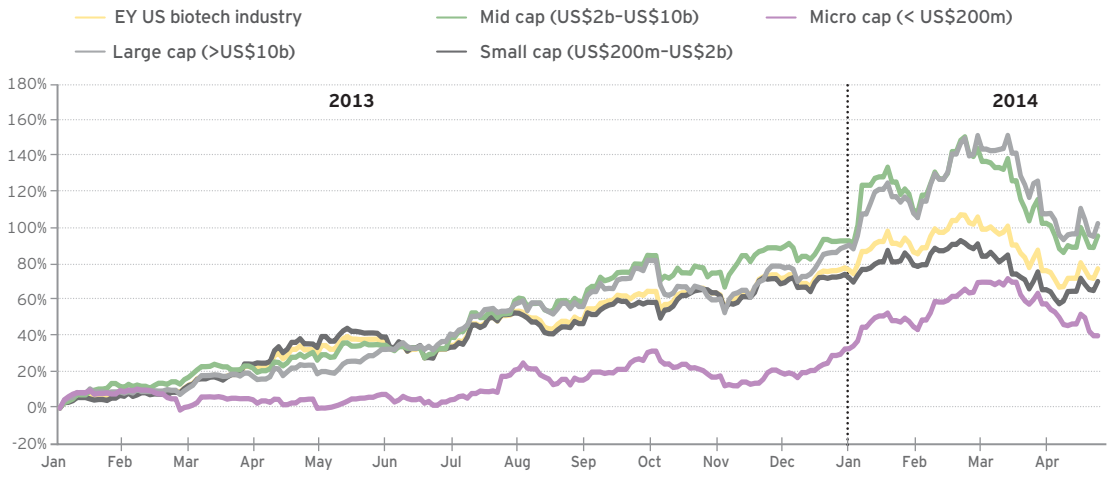
In both the US and Europe, biotech stocks outperformed broader indices, led by large companies

US market capitalization relative to leading indices



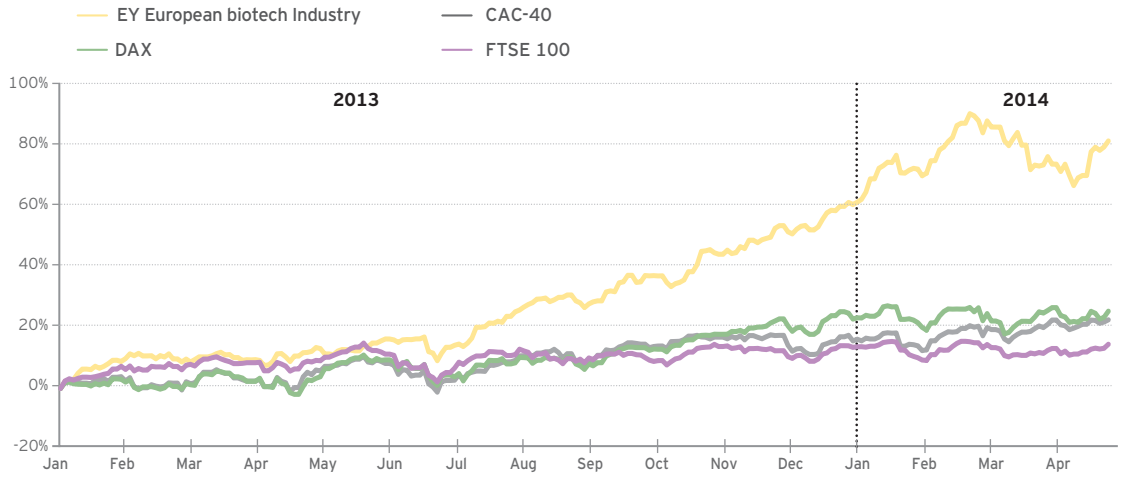
Source: EY and Capital IQ.
Chart includes companies that were active on 30 April 2014.

US market capitalization by company size



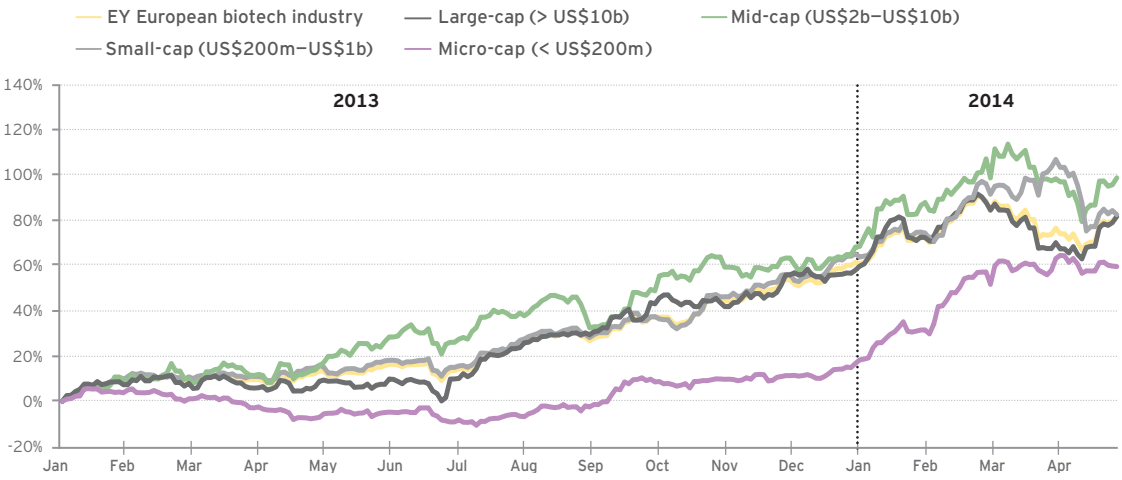
Source: EY and Capital IQ.
Chart includes companies that were active on 30 April 2014.

European market capitalization relative to leading indices



Source: EY and Capital IQ.
Chart includes companies that were active on 30 April 2014.

European market capitalization by company size



Source: EY and Capital IQ.
Chart includes companies that were active on 30 April 2014.

Europe

The situation in Europe was almost a mirror image of that in the US. While the US industry saw strong growth in revenues and R&D spending and a decline in net income, the European sector delivered a relatively weak performance on revenues and R&D spending but came through with strong growth in net income.

European public companies grew revenues by only 3% in 2013 – substantially below both growth in the US (13%) and European growth in 2012 (8%). On a positive note, 75% of European biotech firms generated at least some revenues and 43% of companies grew their top lines. Jazz Pharmaceuticals, which relocated its headquarters to Ireland in 2012, and Eurofins Scientific alone accounted for US$ 572 million in revenue growth in 2013. Jazz experienced high demand for its narcolepsy drug Xyrem (up 50% to US$ 569 million) and leukemia drug Erwinaze/Erwinase (up 32% to US$ 174 million).

European R&D spending dropped 4% in 2013. While 55% of European companies increased their R&D spending – almost the same proportion seen in the US – their uptick was relatively modest and was counteracted by significant cuts at a number of companies. These included a US$ 77 million cut in spending by NeuroSearch (which announced in March 2013 that it would begin winding up its activities) and US$ 50 million in cuts each by Shire (the result of a restructuring program) and Actelion (to refocus on marketing its FDA- and EMA-approved endothelin receptor antagonist, macitentan – a possible successor to its blockbuster Tracleer – and on deals related to specialty medicines).

European biotechnology at a glance, 2012–13 (US$ m)

	2013	2012	% change
Public company data			
Revenues	20,959	20,397	3%
R&D expense	4,834	5,020	-4%
Net income (loss)	1,033	184	462%
Market capitalization	115,131	80,098	44%
Number of employees	55,030	52,540	5%
Financing			
Capital raised by public companies	4,231	2,972	42%
Number of IPOs	8	3	167%
Capital raised by private companies	1,484	1,295	15%
Number of companies			
Public companies	168	169	-1%
Private companies	1,915	1,934	-1%
Public and private companies	2,083	2,103	-1%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

While US biotech companies' aggregate net income declined, their counterparts in Europe saw net income soar by US$ 849 million in 2013 – a 462% increase in which 84 public companies saw gains on the bottom line. Of the gainers, Ipsen was the biggest, up US$ 240 million, followed by Actelion, up US$ 165 million. But gains in net income were not common to all European commercial leaders. Shire's net income dropped by US$ 80.3 million, Jazz Pharmaceuticals' by US$ 72.3 million, QIAGEN's by US$ 60.4 million and Meda's by US$ 54.8 million.

Like their counterparts in the US, European biotech companies saw their market capitalizations soar amid positive investor sentiment – though not nearly to the same extent as in the US. Two-thirds of European companies saw their market caps increase in 2013.

The European results were skewed by the acquisition of Elan. Normalized for this acquisition, revenues would have increased by 9% instead of 3%. R&D expense would have declined by 1% instead of 4% and market capitalization would have increased by 56% instead of 44%.

Splitting the European biotech sector into its commercial leaders and smaller companies paints a somewhat dispiriting picture. European commercial leaders lag behind their US counterparts in most categories – a 4% increase in revenues, against 15% in the US, and no growth in R&D spending, despite better performance in net income than the US.

European biotechnology: commercial leaders and other companies, 2012–13 (US$ m)

	2013	2012	US$ change	% change
Commercial leaders				
Revenues	17,046	16,413	633	4%
R&D expense	2,729	2,726	3	0%
Net income (loss)	2,278	1,987	291	15%
Market capitalization	77,924	52,787	25,138	48%
Number of employees	42,367	38,952	3,415	9%
Other companies				
Revenues	3,924	4,003	(80)	-2%
R&D expense	2,117	2,315	(198)	-9%
Net income (loss)	(1,234)	(1,783)	550	-31%
Market capitalization	37,253	27,378	9,875	36%
Number of employees	12,685	13,619	(934)	-7%

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

European commercial leaders, 2009-13

2009 8 companies	2010 8 companies	2011 8 companies	2012 9 companies	2013 9 companies
Actelion	Actelion	Actelion	Actelion	Actelion
Elan Corporation	Elan Corporation	Elan Corporation	Elan Corporation	Acquired by Perrigo
Organic growth and relocation from USA to Ireland →				Alkermes
Eurofins Scientific	Eurofins Scientific	Eurofins Scientific	Eurofins Scientific	Eurofins Scientific
Ipsen	Ipsen	Ipsen	Ipsen	Ipsen
Organic growth and relocation from USA to Ireland →			Jazz Pharmaceuticals	Jazz Pharmaceuticals
Meda	Meda	Meda	Meda	Meda
Novozymes	Novozymes	Novozymes	Novozymes	Novozymes
QIAGEN	QIAGEN	QIAGEN	QIAGEN	QIAGEN
Shire	Shire	Shire	Shire	Shire

Source: EY, Capital IQ and company financial statement data.
Commercial leaders are companies with revenues in excess of US$ 500 million.

Alkermes joined the European commercial leaders group, based upon the continued strength of its antipsychotic franchise and its alcohol dependency drug naltrexone. The number of European commercial leaders remained nine, as in 2012.

Selected European biotechnology public company financial highlights by country, 2013 (US$ m, % change over 2012)

Country	Number of public companies	Market capitalization 31 Dec 13	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term investments	Total assets
United Kingdom	30 -3%	32,825 54%	5,774 5%	1,217 -5%	547 -9%	3,054 39%	10,652 12%
Israel	26 8%	3,259 58%	173 30%	142 1%	(159) 2%	591 90%	867 109%
Sweden	24 -8%	9,451 51%	2,627 6%	658 2%	34 669%	338 -2%	7,281 4%
France	23 5%	11,532 41%	3,919 13%	692 11%	(1) -99%	978 10%	5,105 17%
Germany	13 0%	3,469 74%	286 8%	147 -19%	(108) -59%	409 3%	1,070 17%
Norway	9 0%	3,070 96%	157 -6%	59 18%	(94) 827%	312 59%	508 30%
Denmark	9 13%	15,766 59%	2,463 8%	541 -7%	339 185%	412 -3%	3,719 8%
Switzerland	8 0%	10,614 71%	1,989 4%	556 -14%	382 135%	1,327 -19%	3,779 10%
Belgium	6 0%	2,483 -31%	423 14%	254 19%	(59) 3%	734 61%	1,098 30%
Netherlands	3 0%	5,813 33%	1,323 3%	184 25%	27 -67%	512 4%	4,251 2%
Other	17 -11%	16,850 15%	1,827 -28%	384 -25%	124 -167%	1,553 -13%	5,572 5%
Total	**168** **-1%**	**115,131** **44%**	**20,959** **3%**	**4,834** **-4%**	**1,033** **462%**	**10,220** **12%**	**43,901** **10%**

Source: EY and company financial statement data.
Percent changes refer to change over 31 December 2012. Numbers may appear inconsistent because of rounding.

Canada

Revenues of Canadian biotech companies grew by 3% in 2013, up from 1% in 2012. Paladin Labs, a specialty pharma, achieved the biggest growth, up 28% to US$ 269 million. In November 2013, the company entered into an agreement to merge with Endo Health Solutions; the US$ 2.7 billion deal was finalized in February 2014.

Net incomes across Canadian biotech were down 26% in 2013, a deterioration from 2012's 18% increase. R&D spending was down 13% overall in 2013, led by cuts at Oncolytics Biotech, QLT and Cardiome Pharma. The sector's market capitalization rose by 36% after a decline in 2012, well ahead of the 8% market cap growth in the overall Canadian market.

Canadian biotechnology at a glance, 2012–13 (US$ m)

	2013	2012	% change
Public company data			
Revenues	591	573	3%
R&D expense	315	360	-13%
Net income (loss)	(236)	(318)	-26%
Market capitalization	5,616	4,144	36%
Number of employees	1,910	1,940	-2%
Number of companies			
Public companies	59	65	-9%
Private companies	169	169	0%
Public and private companies	228	234	-3%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

Australia

The Australian biotech sector's revenues grew by 6% in 2013, continuing their 2012 trajectory. As always, it is important to note that the vast majority of those revenues – 93% this year – were generated by one company, CSL, whose top line was US$ 4.95 billion. CSL is also responsible for US$ 1.2 billion of the Australian industry's net income and 85% of its market capitalization.

That said, the other 51 companies in the Australian biotech sector had combined revenues of US$ 366 million in 2013, which was a 22% increase on 2012. Net income for this cohort was also up by 8%. Meanwhile, R&D spending for all Australian biotechs remained essentially flat at US$ 644 million.

Australian biotechnology at a glance, 2012–13 (US$ m)

	2013	2012	% change
Public company data			
Revenues	5,316	4,998	6%
R&D expense	644	594	8%
Net income (loss)	962	770	25%
Market capitalization	38,111	33,192	15%
Number of employees	12,380	11,010	12%
Number of companies			
Public companies	50	52	-4%

Source: EY and company financial statement data.
Numbers may appear inconsistent because of rounding.

Financing

Financing

A biotech bounce

The big picture

A year, it turns out, is a long time in biotechnology. In the last issue of *Beyond borders*, we described "the same old new normal," and a financial picture that was stable overall except for a large reduction in debt funding. The downward dip in capital raised in 2012 sharply reversed course in 2013, resulting in the biotech industry's second-highest total capital raise – US$ 31.6 billion – since 2003. Importantly for the overall health of the sector, all sources of financing (other than debt) contributed to this turnaround. Indeed, a historic bull market fed investors' appetite for both initial public offerings and follow-on offerings, while on the private side, venture investment held steady. It's a new normal biotech companies and their investors could easily get used to.

Multiple trends coalesced in 2013 to bring the biotech market back in favor in the US. Despite the botched rollout of the Affordable Care Act, the greater certainty around the implementation of health care reforms has been seen as neutral or a net positive for biopharma companies. A record 39 new drug approvals by the U.S. Food and Drug Administration in 2012 restored investor confidence in the sector, and this buoyancy continued in 2013 with the creation of another expedited approval pathway – the Breakthrough Therapy Designation program – for drugs for serious unmet medical needs. (See "Products and pipeline" on page 87.)

New product launches and creative deal making from biotech stalwarts in 2013 further reinforced investors' enthusiasm. As investors' confidence in biotech flourished, so did their willingness to commit capital to the sector. As we noted in "Financial performance," this newfound optimism arrived just as broader optimism in the markets returned, creating a positive feedback loop that sent biotech stock indices on an upward trend not seen since the 1990s.

The upshot? In 2013, enthusiasm for biotech equities didn't just trickle down to new offerings, it gushed. For the first time since 2008, the public markets were wide open for biotech IPOs. Forty-one biotechs debuted on the US public markets this past year, raising US$ 3.5 billion. That's a 300% increase from 2012 and the highest one-year total since 2000, when 49 companies floated to raise US$ 4.3 billion.

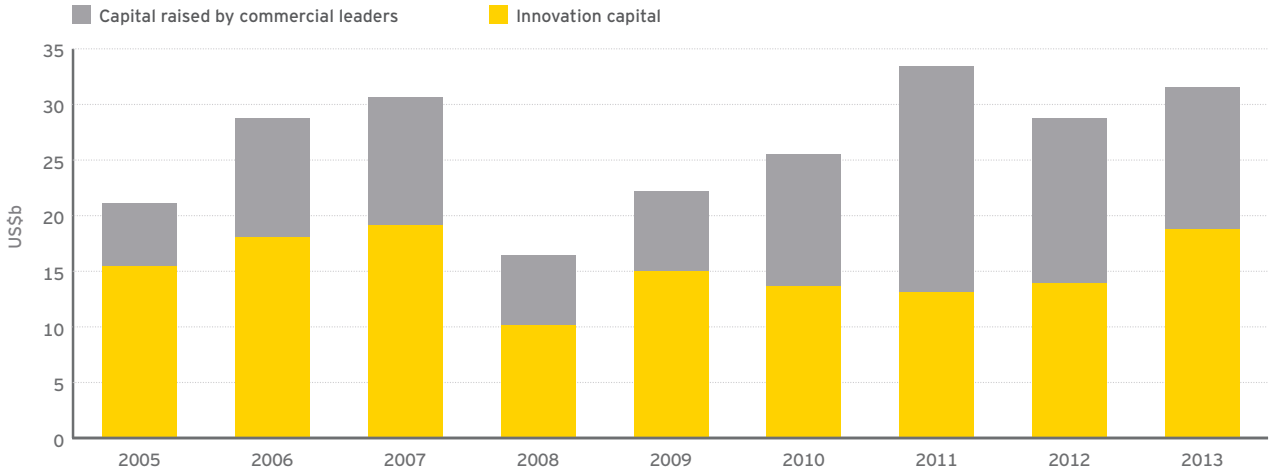
Capital raised in North America and Europe by year (US$ m)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
IPOs	484	2,104	1,900	1,995	2,267	116	840	1,324	858	880	3,521
Follow-on and other	6,043	7,265	7,141	10,875	9,657	4,336	9,859	6,347	6,316	7,930	9,389
Debt	7,296	6,347	6,050	9,702	10,574	5,785	5,605	12,011	20,462	14,349	12,822
Venture	4,236	5,719	6,035	6,229	8,150	6,220	5,913	5,879	5,816	5,547	5,829
Total	**18,058**	**21,435**	**21,126**	**28,802**	**30,648**	**16,456**	**22,217**	**25,560**	**33,452**	**28,706**	**31,562**

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

Largely due to the strength of the US IPO market, 2013 marked a significant increase – 36% – in the amount of innovation capital raised. Interestingly, capital raised by commercial leaders, defined as entities with revenues greater than US$ 500 million, fell by 14% to US$ 12.8 billion during the year, making 2013 the first year since 2010 in which innovation capital was the largest contributor to the financing total.

Innovation capital in North America and Europe by year



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

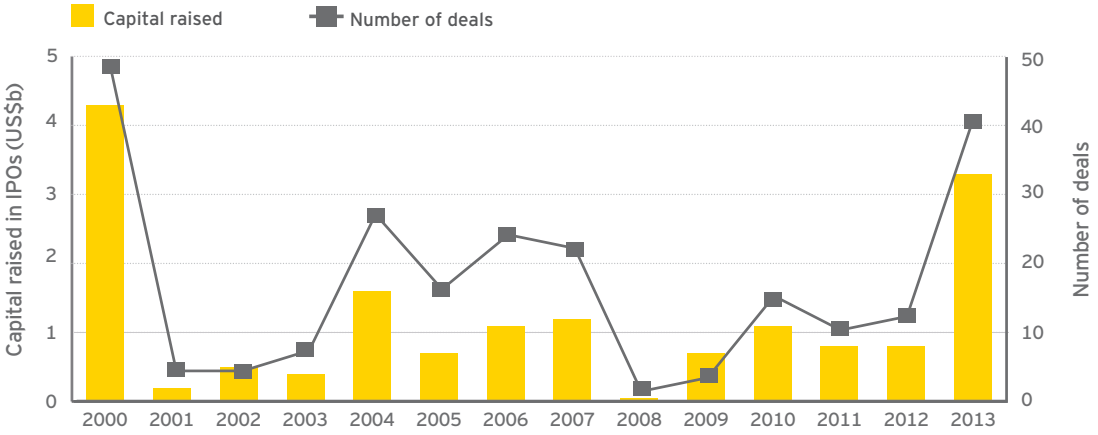
Eyeing the IPOs

Of the 49 companies that debuted in the US and Europe in 2013, 42 were therapeutics companies, three were diagnostics firms, and the remaining organizations focused on animal health, synthetic biology, medical food and research supplies. Action was primarily focused in the US: of the US$ 3.5 billion raised in IPOs, 91% was concentrated in the US. Indeed, just eight European companies went public in 2013, raising a total of US$ 254 million. Three of those – Alcobra, Enzymotec and Prosensa – sought listings on the US' NASDAQ rather than exchanges in Europe.

And yet, the fact that even five companies debuted on exchanges in Europe could be a sign of a 2014 IPO thaw on that continent. Recall that in 2012, only 12 companies went public in the US. Generally speaking, it takes 12 months for equity activity in the US to migrate eastward, in part because generalist and small-cap investment funds are the primary sources of funding in Europe and these groups have traditionally eschewed early-stage biotech companies. Indeed, the record-breaking March 2014 debut on the London Stock Exchange of Circassia, which is developing a cat allergy compound, has given VCs and other European private biotechs hope that markets such as France and Switzerland may open up as well.

In the five years prior to 2013, only six US IPOs managed to tip the US$ 100 million mark. In 2013 alone, nine companies beat that figure. More than 50% of the US-based IPO class had products in Phase II at the time of their offerings, and another 23% had compounds in pivotal trials. By contrast, over 40% of the European biotechs had drugs in Phase III development at the time of their IPOs. That so many companies tapped the equity markets in the US with only proof-of-concept data is hardly surprising. In a healthy market, Phase II is a sweet spot for IPOs: companies have enough efficacy data to lend credibility to their "value" stories, while investors see an opportunity for that value to increase as pivotal data emerge – especially if management teams invest in matters of evidence that set the stage for a lucrative partnering or acquisition deal.

US biotechnology IPOs by year



Source: EY, Capital IQ, BioCentury and VentureSource.

Still, for venture investors, the appetite in the US market for riskier, earlier-stage assets was a welcome change from the recent past. Twelve of the 22 biotechs that went public in the years 2011 and 2012 had lead assets in Phase III or later stages of development, while just four were in Phase II. Such was the strength of 2013's bull market that even a preclinical stage company, Agios Pharmaceuticals, got out.

Boom times for biotech – but for how long?

Even as the biotech industry celebrates the 2013 IPO results, the question on many people's minds is whether this strong showing can be sustained for the remainder of 2014. Since the early 1990s, the biotech industry has seen only five other four-quarter periods in which more than 30 IPO transactions closed. Based on EY's analysis, the four quarters after each of those periods saw a marked decline in public offerings, with an average of 55% fewer deals. How will this recent IPO run-up compare?

The answer depends on one's definition of when in 2013 the IPO window actually opened. If the window opened in January 2013, then the activity seen in the first quarter of 2014 – when 35 biotech companies in the EU and North America went public raising an

additional US$ 2.5 billion – bucked the historically expected decline. However, given that only four companies listed during the first quarter of 2013, it's probably more appropriate to mark the IPO window's opening in the second quarter of that year. Seventeen companies debuted on European and US exchanges in the second quarter of 2013, with 80 companies listing from 1 April 2013 to 31 March 2014. IPO momentum has definitely dissipated in the second quarter of 2014: since 1 April 2014, only nine companies went public on US and European exchanges between that date and 1 June 2014 and they generated a modest US$ 402 million. Thus, while the IPO window may not have slammed shut, unless there is a big uptick later in 2014, it appears the market for new listings may have taken a pause.

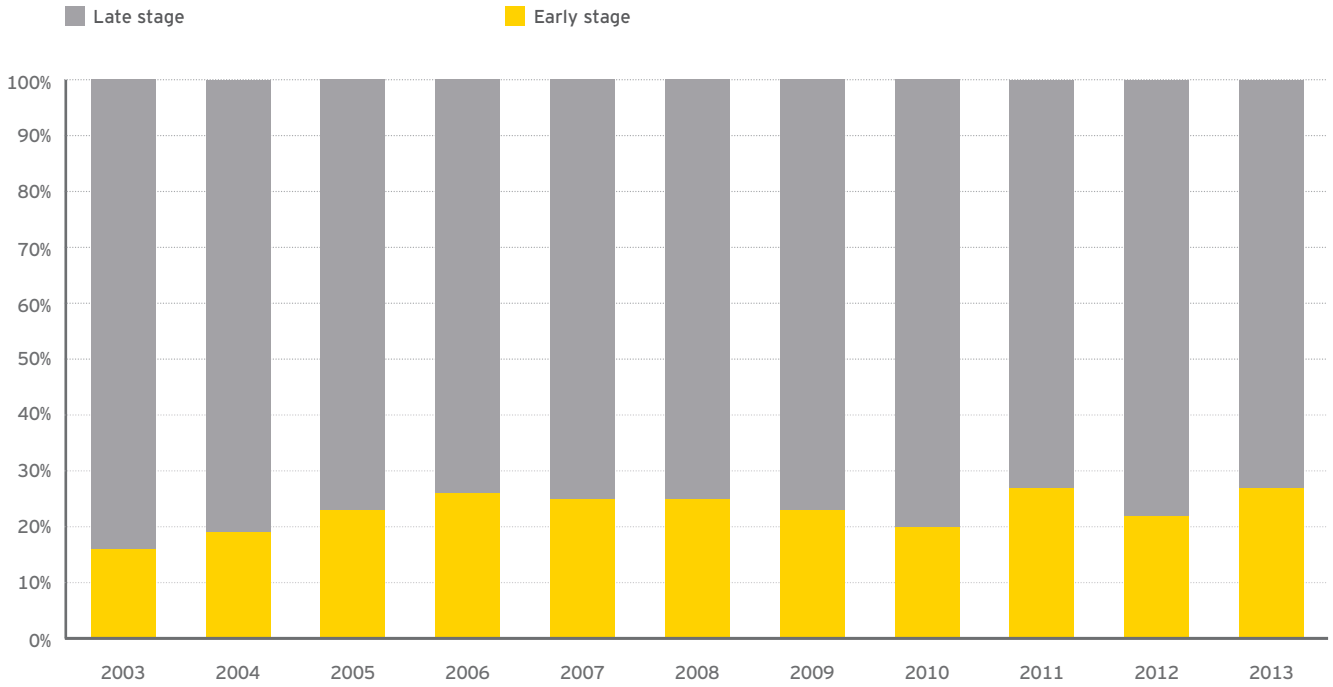
2000 to 2013: what's the difference?

It's natural to want to compare the 2013 class of IPOs with that of 2000, the last big boom time. While the surge in 2000 was mostly fuelled by excitement about the coming molecular genetics era, the 2013 uptick had more to do with the strong commercial success of many of the sectors' bellwether companies as well as the large number of biotechs in the backlog that had been waiting for favorable market conditions to return. In addition, the monetary policies of the U.S. Federal Reserve played a role in 2013 market dynamics by encouraging investors to seek returns through investment in higher-risk sectors.

A closer look at the kinds of companies that debuted in 2000 versus 2013 shows other important differences. For venture backers, an IPO in 2000 typically represented an exit from venture funding. In today's environment, where it takes longer for companies to achieve liquidity, that is less often the case. Instead, VCs are frequently doubling down on their investments, and VC participation in the IPO is regarded as one mechanism to ensure the success of the offering. In fact, our analysis shows that insiders invested in 71% of the 2013 IPO transactions, with a median investment size of 20% of the IPO shares.

In addition, there's been a shift in the kinds of companies generating investor interest. In 2000, research tools and services companies were in the spotlight, as investors bet new entrants would replicate the deal-making success that data-driven companies such as Millennium Pharmaceuticals and Human Genome Sciences had enjoyed. After the genomics bubble burst, platform tools and

US and European venture investment by round and year



Source: EY, Capital IQ, BioCentury and VentureSource

diagnostics biotechs lost much of their luster; investors saw more potential to create value through the development of therapeutics, and some service-oriented companies reoriented their business models to focus on drug development. That preference for assets has continued in the intervening years. In 2013, therapeutics companies dominated the IPO scene: 86% in 2013, versus 59% in 2000.

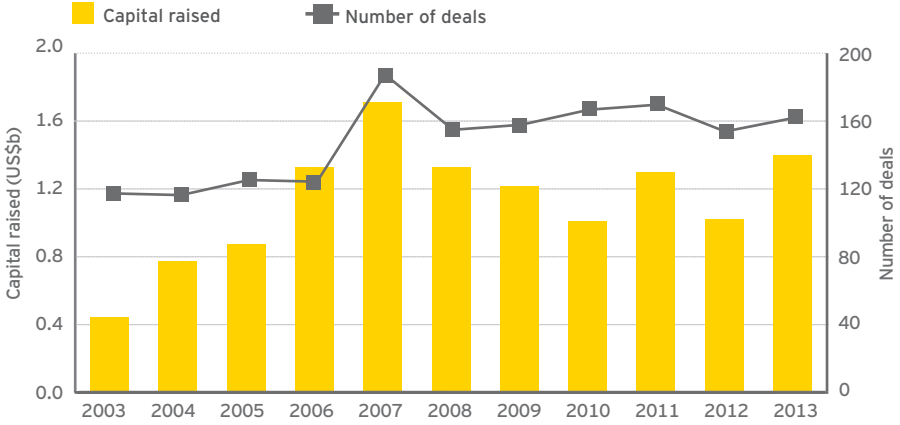
That said, it is worth noting that several of the companies that went to IPO in 2013 (including Agios Pharmaceuticals, Epizyme, bluebird bio and OncoMed Pharmaceuticals) had good stories to tell because of the enabling technology platforms underpinning them. The message is that although perceived value lies in the assets, to access the public markets, it helps to be supported by an R&D discovery engine.

VC holding steady

In 2013, big changes in the IPO, follow-on and debt markets were not mirrored by similar volatility in the biotech venture capital market, which exceeded US$ 5.5 billion for the fifth consecutive year. Early-stage investments, defined as seed and first-round financings, accounted for 26% of the total venture capital investment in biotech in 2013. That's slightly above the 23% average that has held constant since 2003.

A deeper dive into the numbers shows some encouraging signs. Based on EY's analysis, the average 2013 deal size – at US$ 8.6 million – was the highest since 2007. Moreover, total seed and first-round venture capital investments increased in 2013 to US$ 1.4 billion, their highest level since the heady pre-crisis days of 2007.

US and European early-stage venture investment by year



Source: EY, Capital IQ, BioCentury and VentureSource.

United States

US biotechnology financings by year (US$ m)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
IPOs	448	1,565	745	1,133	1,241	6	697	1,097	803	840	3,264
Follow-on and other	4,168	6,221	5,362	7,615	5,734	3,268	7,362	4,289	4,861	6,666	7,401
Debt	6,239	4,745	5,605	7,957	8,877	5,626	4,915	11,505	19,773	11,992	10,277
Venture	2,929	3,543	3,931	3,966	5,948	4,462	4,693	4,398	4,277	4,208	4,311
Total	**13,785**	**16,074**	**15,643**	**20,671**	**21,800**	**13,362**	**17,667**	**21,289**	**29,714**	**23,706**	**25,253**

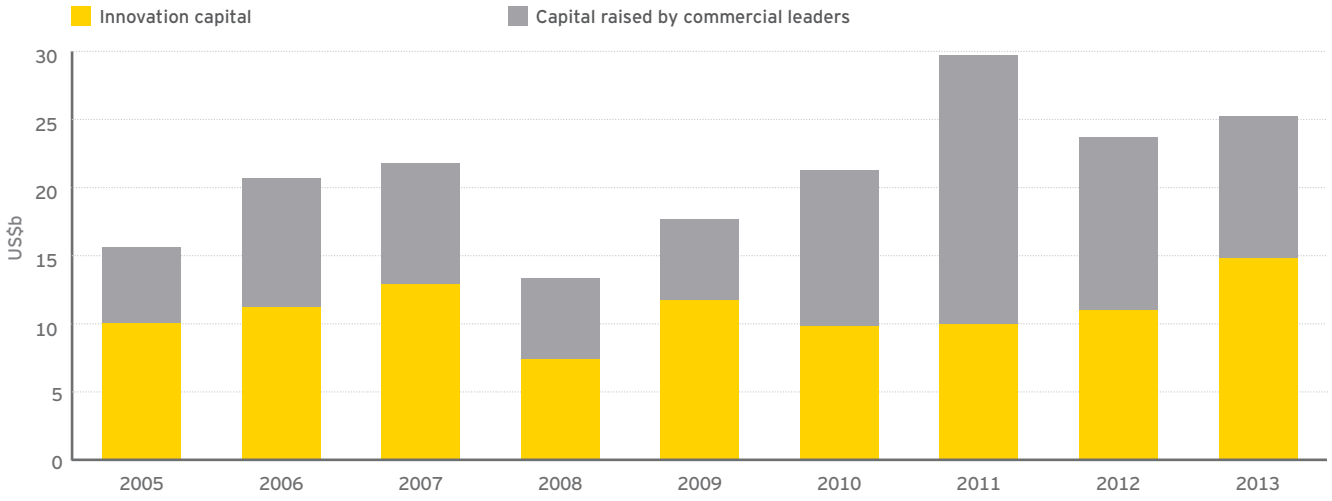
Source: EY, BioCentury, Capital IQ and VentureSource.
Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt."

After a strong showing in follow-on offerings in 2012, in 2013 the public equity markets in the US accelerated to their best performance in over a decade. The total amount brought in by companies in the sector – US$ 25.3 billion – represented a 7% increase year-on-year. Indeed, 2013 was the second-best year for biotech financing since 2003, eclipsed only by the US$ 29.7 billion raised in 2011, two-thirds of which was in the form of debt offerings.

A big driver for the 2013 total was, of course, the public equity markets. The IPO boom was the largest part of that, but follow-on public offerings also reached their second highest total since 2003, driven by 207 financings, including 19 equity offerings that were US$ 100 million or greater in size. Venture capital investing remained a constant for the sixth year in a row, settling into a groove of between US$ 4.2 billion and US$ 4.7 billion annually.

Debt was the only vehicle to decline in 2013 – debt offerings were down 14% year-on-year. However, the picture changes when Amgen and Gilead Sciences are taken out of the data set. Those two companies were responsible for 60% (US$ 26 billion) of all debt offerings between 2010 and 2012, including US$ 15.2 billion in 2011. If we exclude any historic Amgen and Gilead Sciences debt offerings, 2013's US$ 10.3 billion was the highest annual total since 2003.

Innovation capital in the US by year



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

Driven by the strong IPO market, US companies raised US$ 14.8 billion in innovation capital in 2013 – the largest amount in any year in the last decade, and 59% of the total capital raised. Meantime, the commercial leaders raised US$ 10.5 billion in 2013, despite a drop in debt of nearly 50% since 2011.

Quarterly breakdown of US biotechnology financings (US$ m), 2013

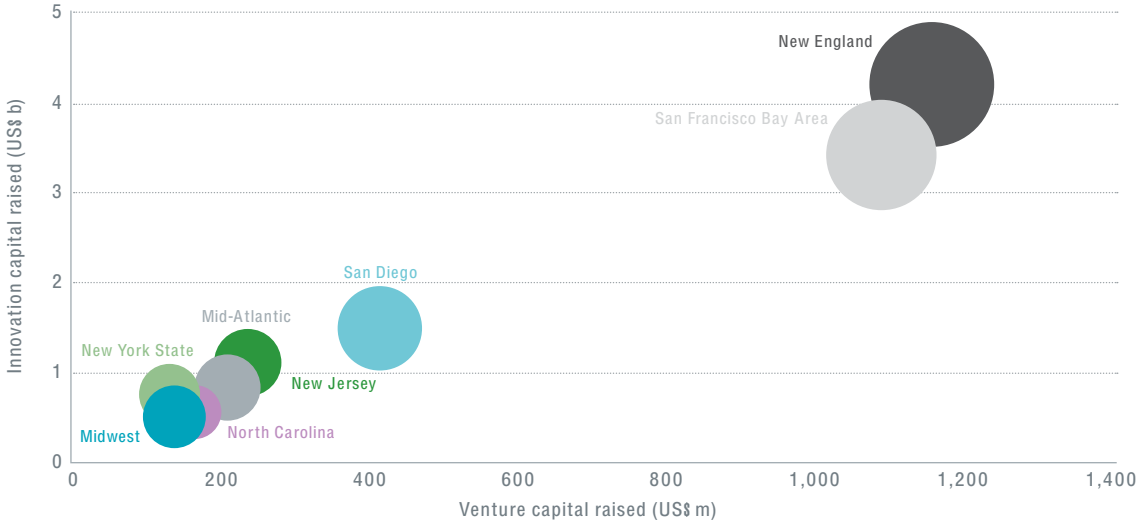
	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	$ 173 (3)	$ 1,078 (13)	$ 1,197 (13)	$ 817 (12)	$ 3,264 (41)
Follow-on and other	$ 2,518 (54)	$ 1,835 (54)	$ 1,621 (51)	$ 1,428 (48)	$ 7,401 (207)
Debt	$ 1,438 (36)	$ 1,693 (29)	$ 2,719 (35)	$ 4,427 (32)	$ 10,277 (132)
Venture	$ 1,041 (94)	$ 1,095 (116)	$ 991 (84)	$ 1,184 (77)	$ 4,311 (371)
Total	**$ 5,170 (187)**	**$ 5,701 (212)**	**$ 6,527 (183)**	**$ 7,855 (169)**	**$ 25,253 (751)**

Source: EY, BioCentury, Capital IQ and VentureSource.
Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.

The first quarter of 2013 saw a very strong market in follow-on offerings, including significant raises by Onyx Pharmaceuticals, ARIAD Pharmaceuticals and Pharmacyclics, which helped pry open the long dormant IPO window. After a tepid first quarter, the IPO market exploded in the second quarter and remained robust into 2014 as companies took advantage of the first favorable market conditions in many years.

Debt offerings also rebounded in the second half of the year. Notable deals included Celgene's US$ 1.5 billion debt offering for further development of its pipeline, as well as general corporate development. Salix Pharmaceuticals tapped the debt market twice in 2013, raising nearly US$ 2 billion to support its acquisition of Santarus and the creation of the largest gastroenterology-focused specialty pharma firm in the US.

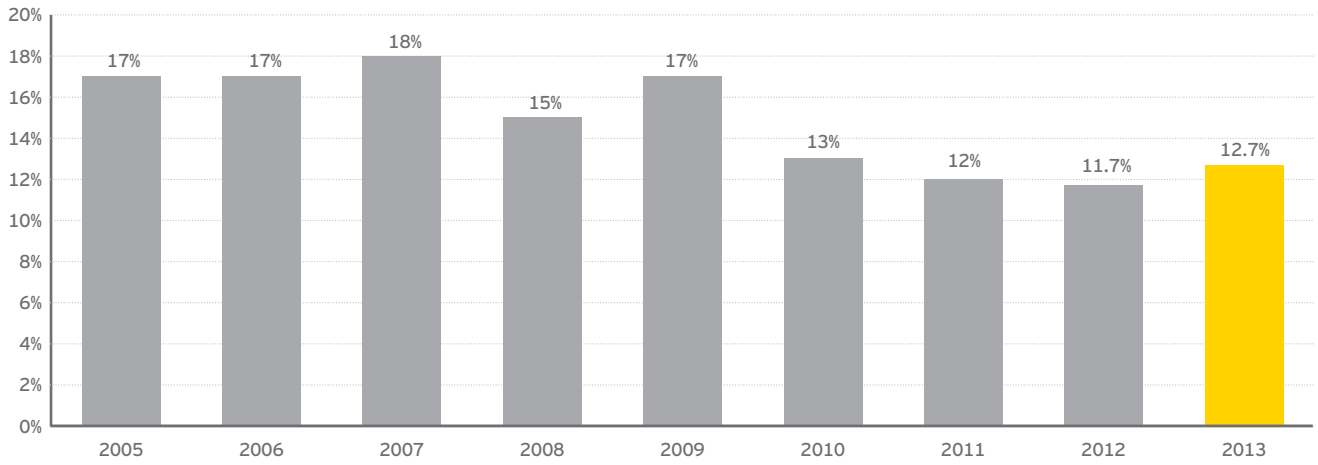
Capital raised by leading US regions, 2013



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

In 2013, the three leading clusters that raised the most innovation capital were, not surprisingly, New England, the San Francisco Bay Area and San Diego. Together these three regions captured US$ 9.1 billion of the US$ 14.8 billion in innovation capital raised. Those three regions were also targets for 60% of the venture capital raised nationally (83 deals for US$ 1.2 billion in New England; 72 deals for US$ 1.1 billion in the Bay Area; and 56 VC deals raising US$ 414 million in San Diego).

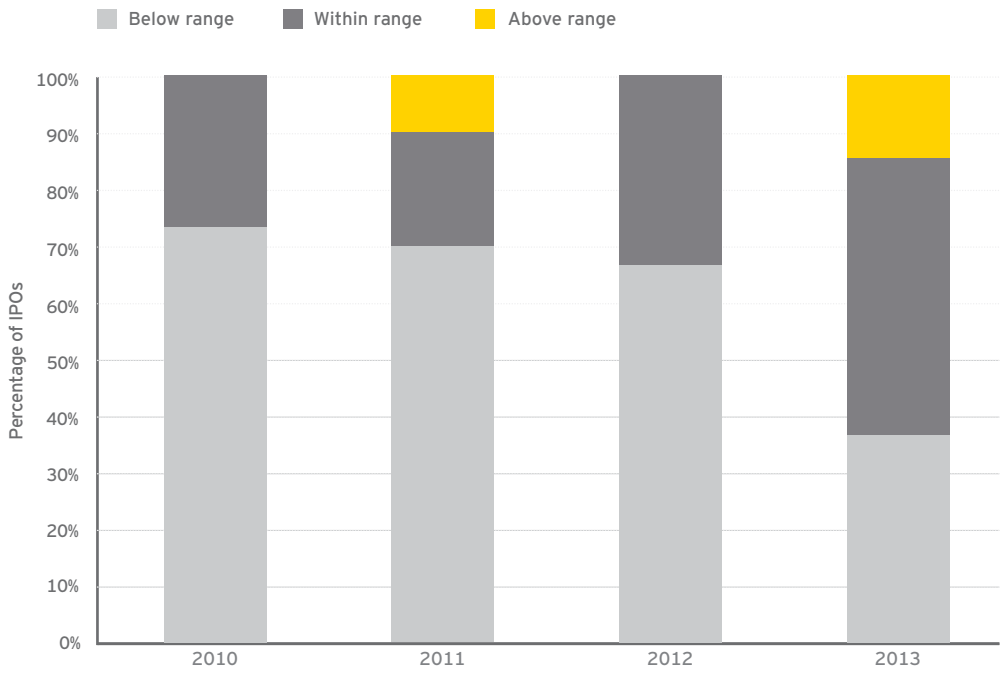
US biopharmaceutical venture capital as a share of total venture capital by year



Source: VentureSource.

The biotech industry's share of total US venture capital grew slightly from 2012 totals, from 12% to 12.7%, but remains well below the 17%-18% of total venture funding it held before the financial crisis.

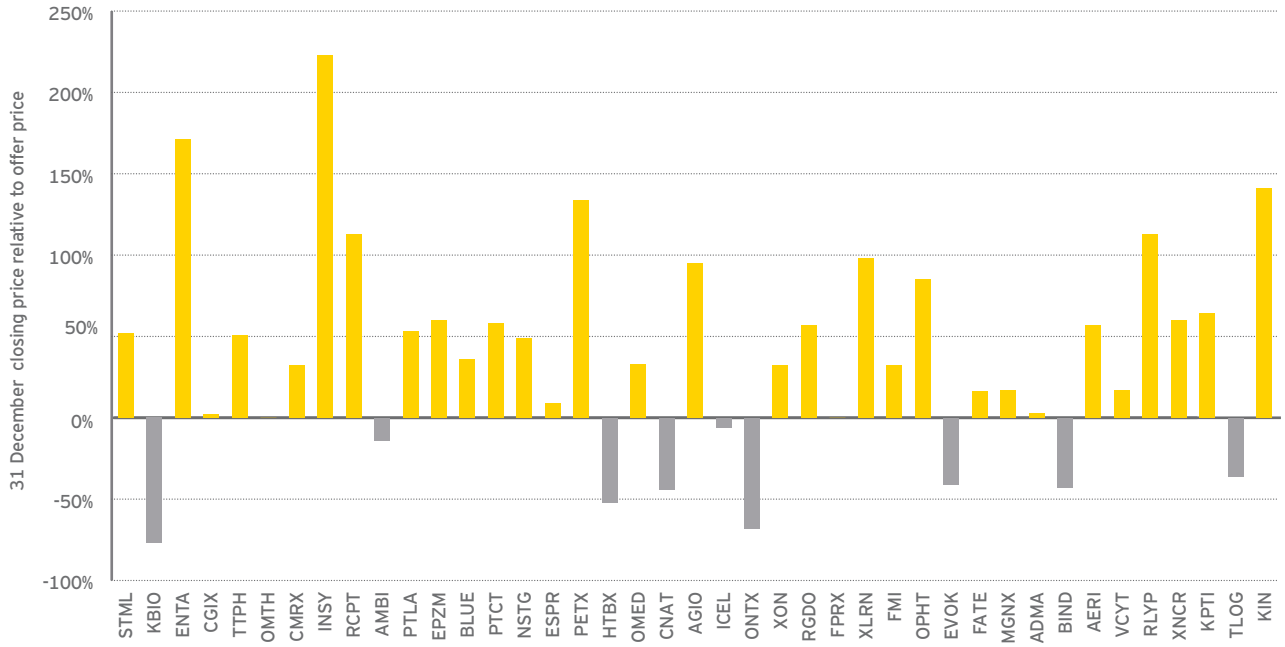
2013 US IPO ranges



Source: EY, Capital IQ, BioCentury and VentureSource.

From 2010 to 2012, close to 70% of the companies that listed on US exchanges priced below their expected ranges. In 2013, this trend sharply reversed course, and as the year advanced, rising demand for IPOs led most companies to price within or above their ranges. Based on EY's analysis, 54% of companies that went public in the second quarter of 2013 priced at or above their expected IPO ranges; in the third quarter that percentage grew to 88%.

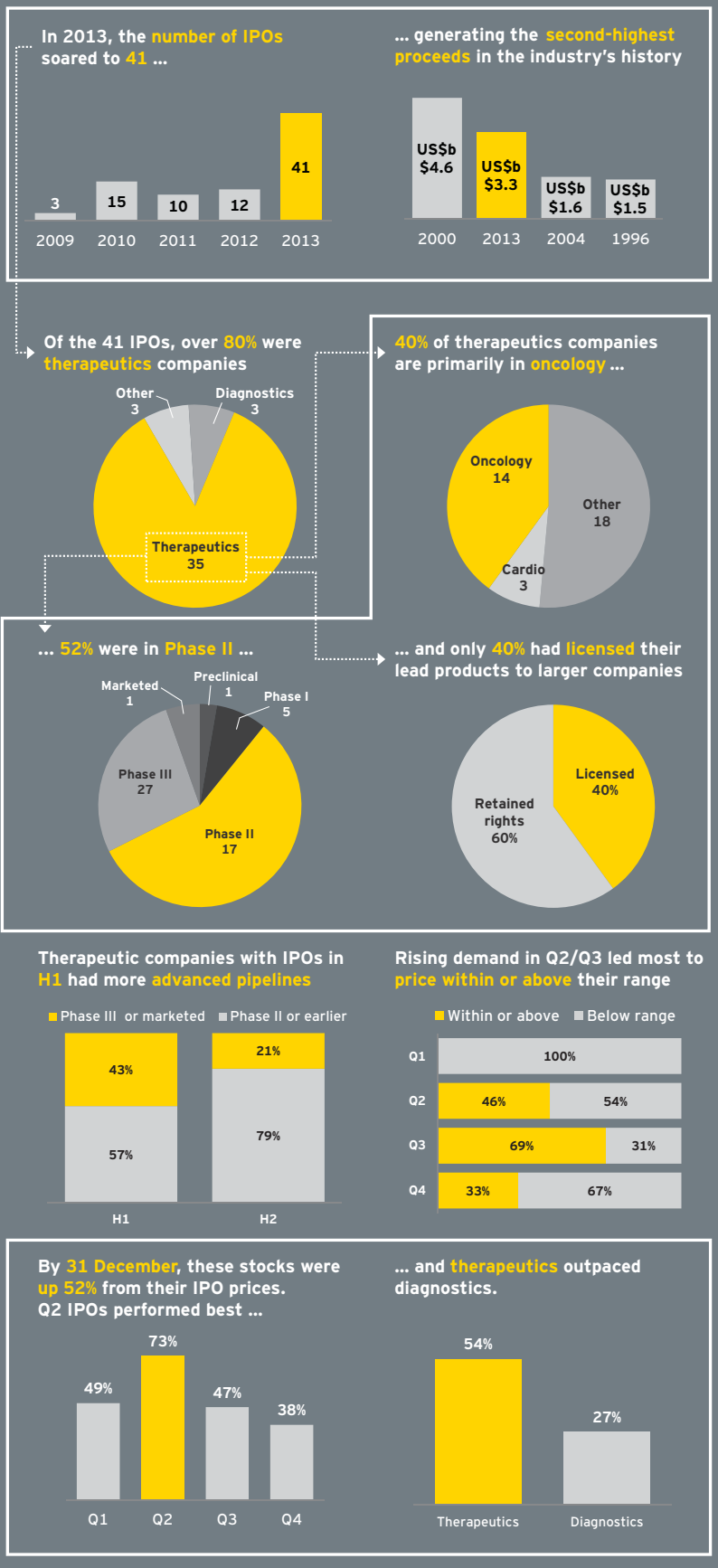
US IPO performance, 2013



Source: EY, CapitalIQ and finance.yahoo.com.

The 2013 IPO boom was marked by the extent to which the newly listed companies continued to return value to investors. In 2013, of the 41 IPOs, 33 outperformed their launch prices by year's end (or earlier date if acquired). Nine hit or surpassed the industry average of 80%, and five had more than doubled their IPO prices. In aggregate, an investor who purchased one share of each IPO would have had a return of 48% by 31 December 2013 and those returns have continued to rise at the same rate through 30 May 2014.

The 2013 US biotech IPO market in 10 charts



Source: EY, CapitalIQ, Biocentury and VentureSource.

Canada

Canadian biotechnology financings by year (US$ m)

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
IPOs	10	0	85	160	9	5	0	0	0	0	0	3
Follow-on and other	318	1,139	435	537	1,589	703	238	633	392	447	316	447
Debt						0	9	3	4	127	349	99
Venture	199	206	271	313	205	352	207	97	87	165	68	44
Total	**527**	**1,345**	**791**	**1,010**	**1,803**	**1,060**	**453**	**733**	**482**	**739**	**733**	**593**

Source: EY, Canadian Biotech News and company websites.
Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt." Separate subtotals for "follow-on and other" and "debt" are not available prior to 2007.

The growth in North American financings stopped at the US border: total financing in Canada, which has not reached US$ 750 million since 2007, was US$ 593 million, down 19% from 2012. Nor did the US IPO boom cause ripples to the north. Antibe Therapeutics, Canada's solitary IPO – the first since 2007 – raised just US$ 3 million. The one glimmer of growth was in follow-on public offerings, which returned to 2011 levels. Venture-backed businesses are typically the growth engine for any sector, but venture capital investment in Canadian biotech hit its lowest point in over 10 years, at just US$ 44 million.

Capital raised by leading Canadian biotech clusters, 2013

Source: EY, Capital IQ, BioCentury and VentureSource.
Size of bubbles shows number of financings per country.

Of the investment that did occur in Canada, Ontario took the honors as the leading destination, attracting 38% (US$ 224 million) of the total investment dollars and 42% (US$ 63 million) of the financing rounds. Quebec (US$ 158 million) and British Columbia (US$ 120 million) were second and third. Trimel Pharmaceuticals and Trillium Therapeutics (formerly known as Stem Cell Therapeutics) brought in the largest financings of the year at US$ 40 million and US$ 33 million respectively.

Quebec attracted US$ 21 million and Ontario US$ 20 million in venture capital. EnGene, a preclinical-stage biopharmaceutical company developing a platform technology for the robust delivery of nucleotides, attracted Canada's largest venture round (US$ 13.3 million).

Europe

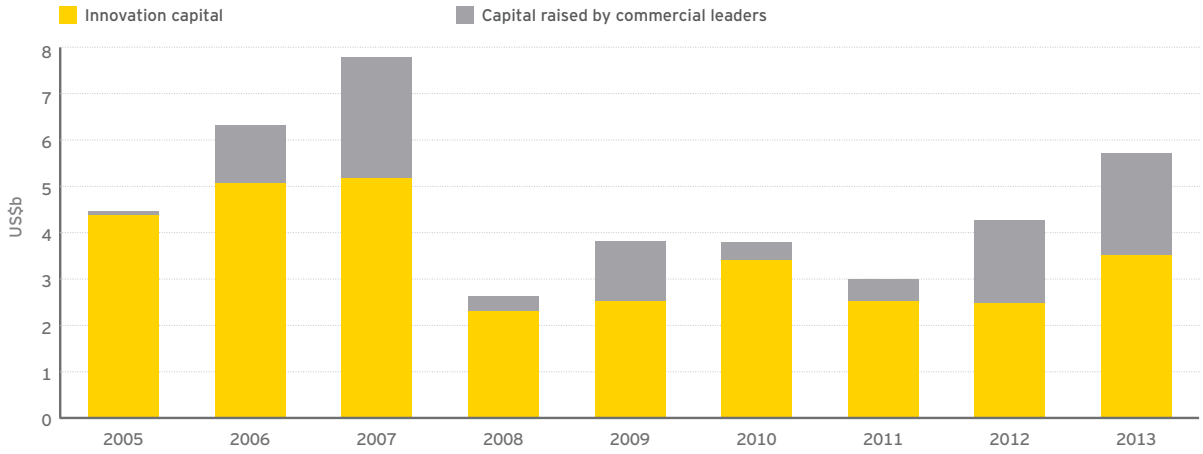
European biotechnology financings by year (US$ m)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
IPOs	36	454	995	853	1,021	111	143	227	55	40	254
Follow-on and other	735	609	1,242	1,672	3,220	830	1,865	1,666	1,008	948	1,541
Debt	1,056	1,602	446	1,744	1,696	150	686	502	562	2,008	2,446
Venture	1,101	1,905	1,790	2,058	1,851	1,551	1,123	1,394	1,374	1,270	1,474
Total	**2,929**	**4,570**	**4,473**	**6,327**	**7,788**	**2,642**	**3,817**	**3,789**	**2,999**	**4,267**	**5,715**

Source: EY, BioCentury, Capital IQ and VentureSource.
Numbers may appear inconsistent because of rounding. Convertible debt instruments included in "debt."

As noted earlier, the European biotech financing picture was very different from that of the US. Total financings for the year increased 34% from 2012 to US$ 5.7 billion – the best figure since 2007. While it was the second strong annual performance in a row, the uptick was not the result of a US-inspired rush on IPO transactions. Almost half of the capital raised in Europe in 2013 came from debt, at US$ 2.4 billion, up from US$ 2 billion in 2012. Jazz Pharmaceuticals, which recently re-domiciled its headquarters following the acquisition of Azur Pharma, and Elan were responsible for two-thirds of that figure. A healthier trend was seen in follow-on public offerings: BTG, Amarin Pharmaceuticals and MorphoSys all inked financings of more than US$ 100 million, helping increase the year-on-year follow-on offerings by US$ 593 million. Venture funding, meanwhile, continued its slow growth from a 2009 drop-off.

European innovation capital by year



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

With fewer commercial leaders than the US, most investment in European biotechnology has typically been in the form of innovation capital. In 2013, US$ 3.5 billion (62% of the total) in innovation capital helped to drive total investment to its highest level since 2007. Meanwhile, commercial leaders saw investment climb to US$ 2.2 billion – another post-crisis high. Private European companies remain under-capitalized compared to their US counterparts, as lower appetite for risk meant VCs and public equity committed fewer dollars to these earlier-stage players. However, the distribution of capital among various European countries continued to be diverse, with some companies, for instances ObsEva, achieving multi-million equity injections in their first venture rounds. In another interesting development, some US VCs are opening European offices, attracted by the variety on offer. San Francisco-based Versant Ventures set up shop in Basel in 2013, and in 2014 invested in local start-ups Anokion and Pqur Therapeutics.

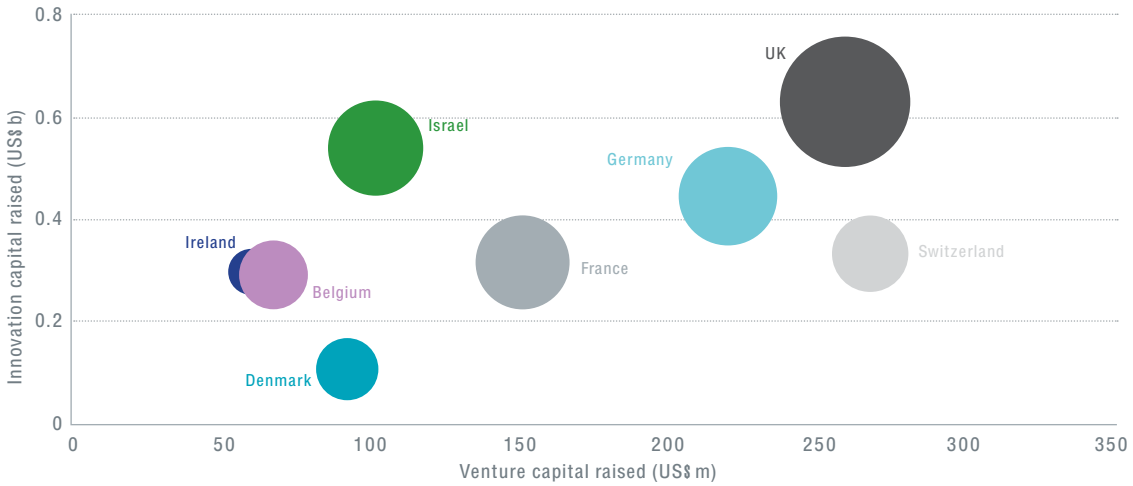
Venture deals peaked in the second quarter thanks to the sizeable financings of Kaiima, Symphogen, Auris Medical and Opsana Therapeutics. Big debt deals from Elan and Jazz Pharmaceuticals drove the spike in European debt raised in the second quarter. Follow-on offerings fluctuated throughout the year, due to the skewing effect of a few large deals such as the healthy raises by BTG, Amarin Pharmaceuticals and MorphoSys.

Quarterly breakdown of European biotechnology financings (US$ m), 2013

	First quarter	Second quarter	Third quarter	Fourth quarter	Total
IPOs	$ 1 (1)	$ 57 (4)	$ 196 (3)	$ 0 (0)	$ 254 (8)
Follow-on and other	$ 286 (29)	$ 470 (13)	$ 562 (18)	$ 223 (28)	$ 1,541 (88)
Debt	$ 439 (14)	$ 1,667 (8)	$ 192 (7)	$ 148 (7)	$ 2,446 (36)
Venture	$ 134 (55)	$ 623 (62)	$ 279 (38)	$ 438 (34)	$ 1,474 (189)
Total	**$ 860 (99)**	**$ 2,817 (87)**	**$ 1,229 (66)**	**$ 810 (69)**	**$ 5,715 (321)**

Source: EY, BioCentury, Capital IQ and VentureSource.
Figures in parentheses are number of financings. Numbers may appear inconsistent because of rounding.

Capital raised by leading European countries, 2013

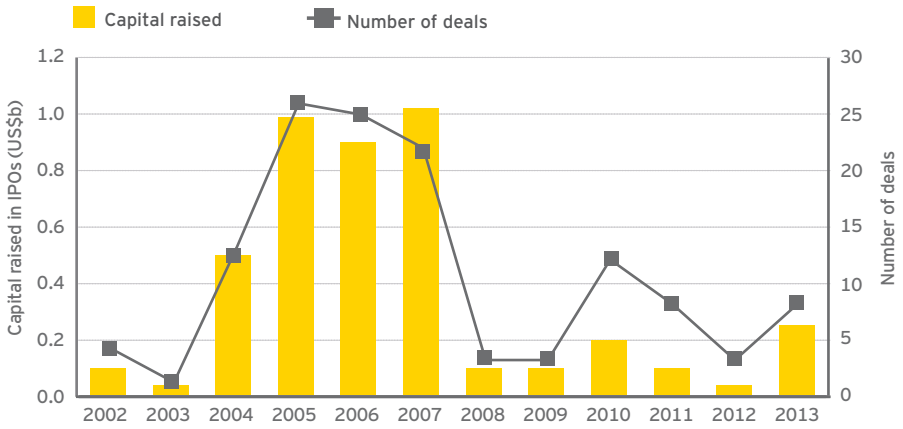


Source: EY, Capital IQ, BioCentury and VentureSource.
Size of bubbles shows number of financings per country.

The UK leads Europe in innovation capital raised with US$ 730 million – a 55% increase over 2012. Israel was second, with US$ 531 million. Israel hosted three of the eight IPOs in Europe, raising US$ 102 million, and the largest single venture round (US$ 65 million for Kaiima).

Meanwhile, with US$ 266 million, Switzerland replaced Germany as the country that attracted the most VC investment in 2013. Switzerland was home to four of the 11 largest VC rounds in 2013, including Auris Medical's US$ 51 million round. The UK (US$ 258 million) and Germany (US$ 217 million) wrapped up the top three.

European biotechnology IPOs by year



Source: EY, Capital IQ, BioCentury and VentureSource.

In 2013, just eight European biotechs had IPOs, raising a modest US$ 254 million. While significantly better than 2011 and 2012, and the highest total since 2007, the European 2013 figure is still well off the averages seen before the financial crisis. That said, the 2014 European IPO market began strongly, with US$ 680 million raised by eight companies in the first quarter.

Of the European companies that listed in 2013, Prosensa (US$ 89.7 million), a Dutch company developing RNA-modulating therapeutics for the treatment of genetic neurological disorders, and Enzymotec (US$ 71 million), an Israeli developer of lipid-based products and solutions for the nutritional and health care markets, notched the two biggest IPOs. In addition to Enzymotec, Israel was home to two of Europe's other 2013 IPOs, Alcobra Pharma and Kadimastem. It is worth nothing that three of the eight European IPOs – Alcobra, Enzymotec and Prosensa – actually chose to list on a US exchange at least in part to access a broader group of biotech investors.

Five of the eight companies outperformed their launch prices. The two biggest winners were Alcobra (125%) and Sweden's Immunicum (311%), a developer of therapeutic cancer vaccines.

Deals

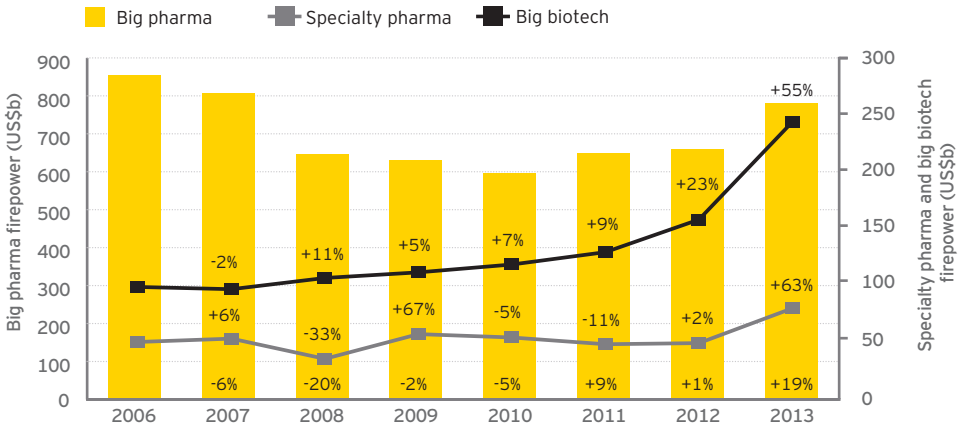
Biotech buyers

The big picture

With big pharmas in a period of revenue growth stagnation, we expected to see an uptick in 2013 in bolt-on acquisitions of biotechs aimed at bolstering their top lines. In reality, that strategy has been hard to implement, resulting in a relatively constant volume of pharma-biotech acquisitions even as the total deal value for such transactions slipped from US$ 20.7 billion (2012) to US$ 12.5 billion (2013). This deal-making restraint was partly due to the rising valuations of public biotechs which placed certain acquisition targets, based on their market capitalizations, out of reach for many potential pharma buyers, including those most in need of growth. The newly opened IPO window, meantime, gave privately held biotech companies a realistic exit option – other than M&A – for the first time since 2007.

In absolute terms, big pharma's purchasing power has continued to rise. However, based on the EY Firepower Index, which aims to measure acquirers' buying ability, this transactional capacity actually decreased in 2013 relative to biotech and specialty pharma. As a result, for any particular transaction, there were more viable competitors in 2013 than in the past. Moreover, in certain cases, big pharmas found themselves at a disadvantage compared to certain specialty pharma acquirers that could afford to offer more for takeover targets because they were domiciled in lower-tax countries.

Relative firepower has decreased for big pharma but increased for specialty pharma and big biotech



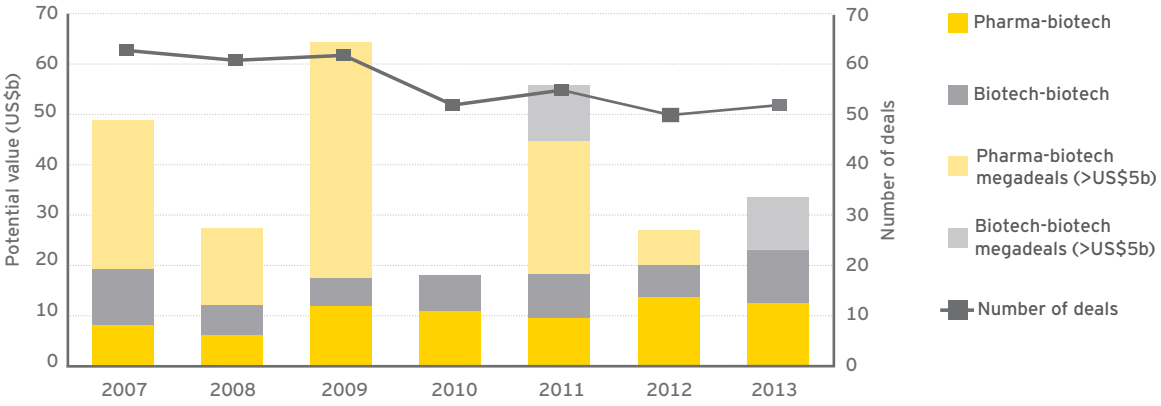
Source: EY and Capital IQ
Data analyzed through 30 April 2014. Percentage change refers to the year-on-year change in firepower.

A closer analysis of 2013 M&A activity shows how those dynamics played out. Interestingly, none of the transactions inked in 2013 with values greater than US$ 5 billion (our defining threshold for "megadeal") involved a big pharma acquirer: OTC player Perrigo captured Elan for US$ 8.6 billion, while Amgen signed one of the biggest acquisitions in its history, purchasing Onyx Pharmaceuticals and its multiple myeloma medicine Kyprolis for approximately US$ 10.4 billion. In terms of total dollars, Thermo Fisher captured honors for the largest deal of the year – and the most expensive takeover since 2011's Sanofi/Genzyme transaction – when it scooped up Life Technologies for US$ 13.6 billion to strengthen its position as a platform tools and technologies provider.

Of the 10 M&A deals in 2013 with potential deal values greater than US$ 1 billion, only three involved a big pharma buyer: Bayer HealthCare/Algeta (US$ 2.9 billion), AstraZeneca/Pearl Therapeutics (US$ 1.15 billion) and Johnson & Johnson/Aragon (US$ 1 billion).

In contrast, it was a strong year for biotech acquirers, with biotech-biotech deal making totaling roughly US$ 21 billion. Admittedly, nearly 50% of that total came from the aforementioned Amgen/Onyx Pharmaceuticals deal.

US and European M&As, 2007-13



Source: EY, Capital IQ, MedTRACK and company news.
The chart excludes transactions where deal terms were not publicly disclosed. Also excluded are two 2013 deals: Thermo Fisher/Life Technologies (US$ 13.6b) and Perrigo/Elan (US$ 8.6b). Neither acquirer qualifies as a pharma or biotech.

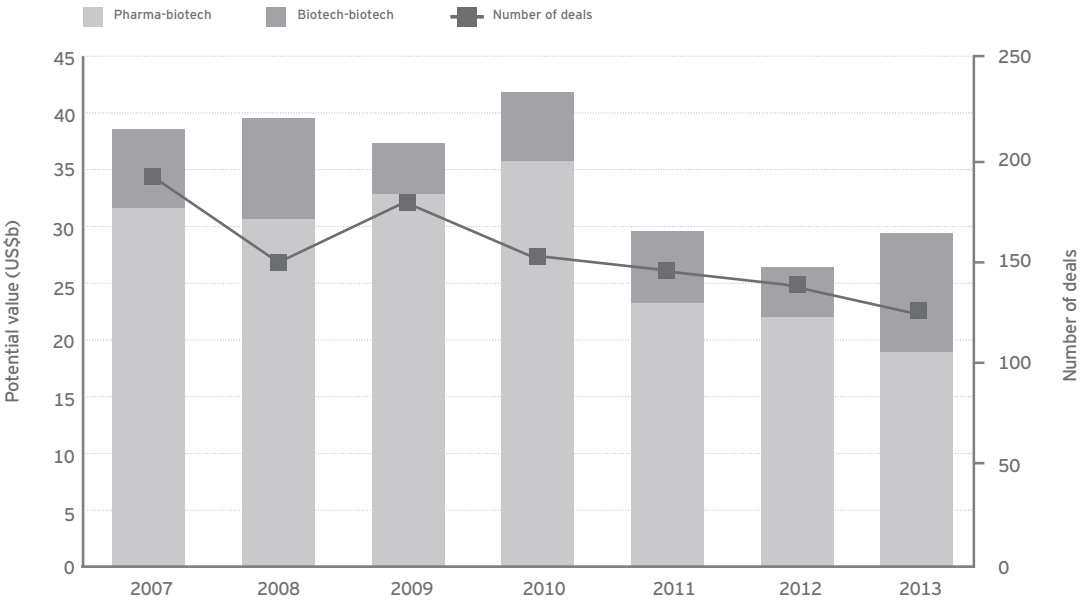
Biotech in-licensing

The growing importance of biotech firepower was evident outside M&A as well. The number of strategic alliances fell for the fourth straight year, representing a 35% drop from 2007's alliance bonanza in which pharmas and biotechs inked nearly 200 deals. Even as alliance volume declined, deal averages increased slightly. On average, 2007 alliances garnered US$ 173.4 million; in 2013, average deal size grew to US$ 180.7 million.

But the numbers begin to tell a different tale when the analysis accounts for which companies – pharmas or biotechs – did the actual in-licensing. Between 2007 and 2013, the average deal value of alliances involving a pharma in-licenser fell from US$ 273.2 million to US$ 258.5 million. During that same period, the average deal value involving a biotech in-licenser nearly doubled, from US$ 81.5 million in 2007 to US$ 160.6 million in 2013.

Meantime, in 2013, the total potential value of all life sciences alliances – the total so-called biobucks – reversed a two-year decline but remained well below historic levels. They increased 11% from 2012, to US$ 29.4 billion. Interestingly, biotech-biotech alliances, which in 2013 totaled US$ 10.5 billion, were entirely responsible for the year-on-year growth in biobucks, as pharma-biotech deal making decreased by US$ 3.1 billion to US$ 18.9 billion. To put that in perspective, that's a 47% drop in the value of pharma-biotech alliance deals from the 2010 peak of US$ 35.7 billion.

US and European strategic alliances based on biobucks, 2007-13



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

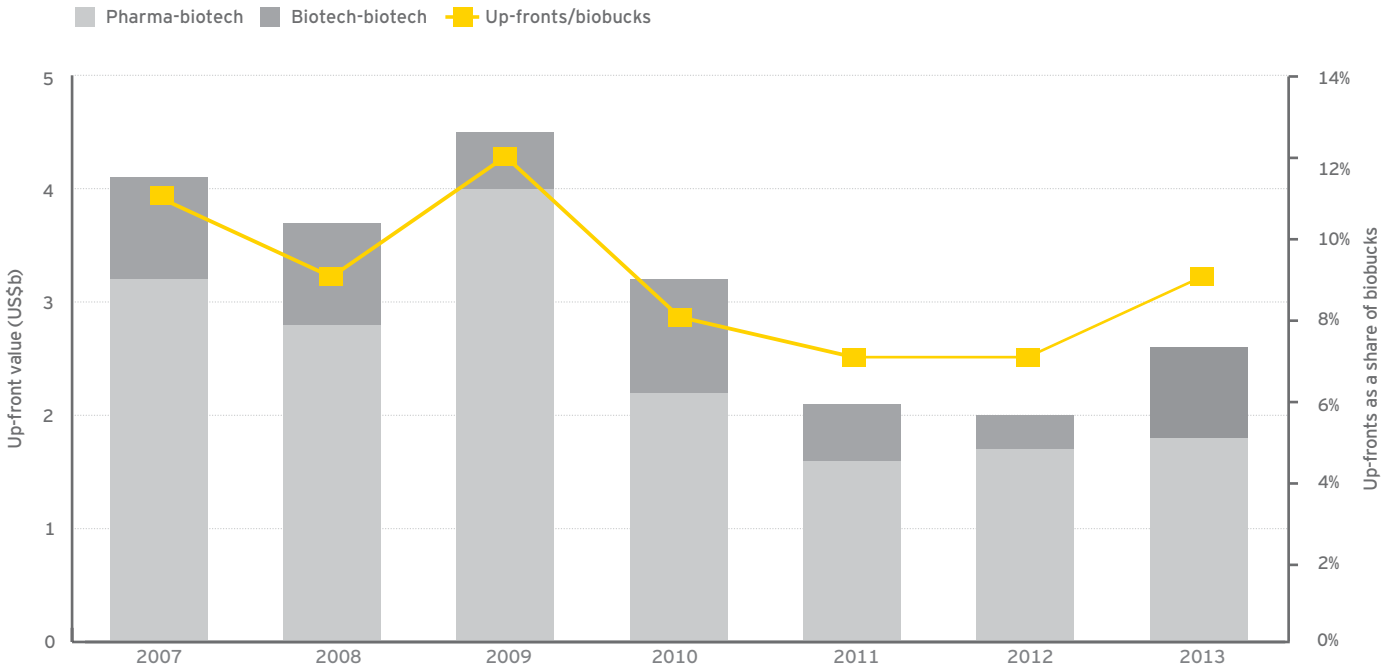
Healthier up-fronts

From 2007 to 2009, biotech licensers captured, on average, 11% of an alliance's potential deal value in the up-front payment. From 2010 to 2012, however, up-front payments as a percentage of deal value dwindled to an average of just 7%.

In 2013, biotech licensers celebrated a 30% year-on-year uptick in total up-front payments for alliances (from US$ 2.0 billion to US$ 2.6 billion) and up-front payments as a percentage of total deal value returned to a healthier 9%. Here again biotech in-licensers played a much bigger role in rewarding their partners in 2013 than they did in 2012. For starters, they committed US$ 500 million more in up-front dollars in 2013 compared to 2012; the average up-front payment also jumped to US$ 25.0 million from US$ 10.6 million.

Meantime, pharma in-licensers spent US$ 1.8 billion on up-front alliance payments, a sum consistent with the trend observed since 2010 and substantially below the levels seen in the 2007-09 time period. That said, in 2013, pharma companies were paying more up front, on average, to access key products and technologies than in prior years: from 2010 to 2012, big pharma up-front fees have averaged around US$ 26.7 million per deal. In 2013, that figure grew to US$ 36.3 million, thanks partly to AstraZeneca's alliances with Fibrogen and ModeRNA Therapeutics, which were worth US$ 350 million and US$ 240 million up front, respectively.

US and European strategic alliances based on up-front payments, 2007–13



Source: EY, MedTRACK and company news.
Chart shows up-front payments for alliances where deal terms are pubicly disclosed.

Notable deals

On the M&A front, outside Amgen's purchase of Onyx Pharmaceuticals, notable transactions by biopharmaceutical acquirers included Shire's US$ 4.2 billion purchase of ViroPharma, Jazz Pharmaceuticals' US$ 1.0 billion acquisition of Gentium and Cubist Pharmaceuticals' deals for Trius Therapeutics (US$ 818 million) and Optimer Pharmaceuticals (US$ 801 million).

The Cubist deals weren't just prominent because of their dollar amounts; they also included sizeable earn-outs. Indeed, despite a robust public market and an alternate exit for privately held players, in 2013 both pharma and biotech acquirers continued to ink deals that included significant downstream milestone payments. Of the 47 biotech acquisitions with publicly available deal terms, 21 (45%) involved some kind of earn-out. Compare that to the pre-financial crisis days of 2007, when only 10 of 58 (17%) acquisitions included downstream milestone payments.

Other 2013 biotech acquisitions involving earn-outs included Amicus Therapeutics' purchase of Callidus Biopharma and Clovis Oncology's buy-up of Ethical Oncology Science. On the pharma side, AstraZeneca was the acquirer most likely to use earn-outs as a key ingredient in its term sheets: not only did the Anglo-Swedish pharma structure its acquisitions of Pearl Therapeutics and Omthera using earn-outs, but its MedImmune division followed suit in its Amplimmune and Spirogen deals.

Madison Dearborn Partners' December 2013 US$ 1.6 billion purchase of Ikaria's commercial assets is also worth mentioning given the relative rarity of private equity-biotech deals. After selling Ikaria and its inhaled nitric oxide delivery system to Madison Dearborn, the original shareholders (which included another private equity firm, New Mountain Capital) chose to purchase a 45% stake in the commercial enterprise while simultaneously creating a new company around the earlier-stage R&D assets.

Deals like Ikaria's split-up are rare but do have precedence: in 2008, Protein Design Labs spun off its R&D capabilities into Facet Biotech to monetize its valuable patent portfolio; as *Beyond borders* went to press, Theravance was in the final stages of separating its R&D and commercial enterprises. Such structures appeal to investors, allowing funders to allocate capital to projects with the risk profiles that appeal to them. It also allows the R&D "newcos" to continue to invest in their pipelines without being constrained by shareholder earnings expectations from the commercial side of the business.

Selected M&As with big up-fronts, 2013

Company	Country	Partner	Country	Up-front payments (US$ m)	Total potential value (US$ m)
Thermo Fisher Scientific	US	Life Technologies	US	13,600	13,600
Amgen	US	Onyx Pharmaceuticals	US	10,400	10,400
Perrigo Company	US	Elan Corporation	Ireland	8,600	8,600
Shire	UK	ViroPharma	US	4,200	4,200
Bayer HealthCare	Germany	Algeta	Norway	2,900	2,900
Endo Health Solutions	US	Paladin Labs	Canada	2,621	2,621
Salix Pharmaceuticals	US	Santarus	US	2,600	2,600
Madison Dearborn Partners	US	Ikaria	US	1,600	1,600
AstraZeneca	UK	Pearl Therapeutics	US	560	1,150
Johnson & Johnson	US	Aragon Pharmaceuticals	US	650	1,000
Jazz Pharmaceuticals	Ireland	Gentium	Italy	1,000	1,000
Allergan	US	MAP Pharmaceuticals	US	958	958
Otsuka Pharmaceutical	Japan	Astex Pharmaceuticals	US	887	887
Cubist Pharmaceuticals	US	Trius Therapeutics	US	701	818
Cubist Pharmaceuticals	US	Optimer Pharmaceuticals	US	535	801

Source: EY, Capital IQ, MedTRACK and company news.
"Total potential value" includes up-front, milestone and other payments from publicly available sources.

In strategic alliances, seven transactions cleared the US$ 100 million up-front threshold in 2013, consistent with 2012 deal flow. In terms of total biobucks, five deals had biobucks greater than US$ 1 billion, again similar to the prior year. Demand for access to platform technologies – and the potential for multi-target collaborations – translated into some of the biggest up-fronts and potential deal values in 2013. ModeRNA Therapeutics (messenger RNA therapeutics), OncoMed Pharmaceuticals (cancer stem cells) and Forma Therapeutics (drug discovery) benefited as big pharmas and big biotechs aimed to secure access to future innovative products.

But promising assets also garnered rich up-fronts in 2013. For instance, AstraZeneca paid US$ 350 million to license rights in selected markets (including the US and China) to FibroGen's late-stage oral anemia therapy. Two next-generation antibody developers also secured valuable up-front payments for late-stage assets: Ablynx partnered its novel, Phase II rheumatoid arthritis therapy to AbbVie for US$ 175 million, while MorphoSys licensed its early-stage anti-CD38 monoclonal antibody to Celgene for US$ 155 million.

Which in-licensers were most active in 2013? On the pharma side, Roche took top honors, notching at least eight deals with disclosed terms worth an estimated US$ 4.8 billion in biobucks. The big biotech Celgene continued to use business development to diversify its pipeline. (See "Celgene: 2013's top deal maker," page 80).

Alliances with big up-front payments, 2013

Company	Country	Partner	Country	Up-front payments (US$ m)
AstraZeneca	UK	FibroGen	US	350
AstraZeneca	UK	ModeRNA Therapeutics	US	240
Celgene	US	OncoMed Pharmaceuticals	US	177
AbbVie	US	Ablynx	Belgium	175
Celgene	US	MorphoSys	Germany	155
Biogen Idec	US	ISIS Pharmaceuticals	US	100
Celgene	US	Acetylon Pharmaceuticals	US	100
Roche	Switzerland	Chiasma	Israel	65
Baxter	US	Cell Therapeutics	US	60
Eisai	Japan	Arena Pharmaceuticals	US	60
Roche	Switzerland	Molecular Partners	Switzerland	59
Amgen	US	Les Laboratoires Servier	France	50
Daiichi Sankyo	Japan	Amplimmune	US	50

Source: EY, MedTRACK and company news.
Table includes only transactions for which up-front payments were publicly disclosed.

Big biobucks alliances, 2013

Company	Country	Partner	Country	Total potential value (US$ m)	Up-front payments (US$ m)
Celgene	US	OncoMed Pharmaceuticals	US	3,332	177
Celgene	US	Acetylon Pharmaceuticals	US	1,200	100
Roche	Switzerland	Molecular Partners	Switzerland	1,138	59
Gilead Sciences	US	MacroGenics	US	1,115	30
Roche	Switzerland	immatics biotechnologies	Germany	1,017	17
Celgene	US	Forma Therapeutics	US	945	ND
AbbVie	US	Ablynx	Belgium	840	175
Celgene	US	MorphoSys	Germany	834	155
AstraZeneca	UK	FibroGen	US	815	350
Astellas Pharma	Japan	Mitokyne	US	730	ND
Pfizer	US	CytomX Therapeutics	US	635	ND
Roche	Switzerland	Prothena Corporation	Ireland	600	45
Roche	Switzerland	Chiasma	Israel	595	65
GlaxoSmithKline	UK	MorphoSys	Germany	592	30
Dainippon Sumitomo Pharma	Japan	Edison Pharmaceuticals	US	545	35

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

Capturing value

Market dynamics and increased competition for innovative assets from a range of potential buyers, especially specialty pharma and big biotech, created a more positive deal-making climate for biotechs in 2013. It's welcome news for smaller biotechs, which as a class are recognizing more value for their R&D efforts. Nevertheless, with M&A earn-outs still prevalent and up-front alliance payments representing just 9% of the total value, we'd argue that even more value could be unlocked as we discuss in the main "Point of view."

Celgene: 2013's top deal maker

As a class, big biotechs stepped up their deal-making activities in 2013. But in terms of volume, monetary size and creativity, one big biotech stood out: Celgene. In 2013, Celgene formed nine alliances worth more than US$ 7 billion, including an option-based tie-up with newly public cancer stem cell player OncoMed Pharmaceuticals potentially worth US$ 3.3 billion and an option to acquire Acetylon Pharmaceuticals, which has a multiple myeloma drug in early clinical development, for US$ 1.2 billion.

From its 2008 alliance with Acceleron Pharma to June 2014, Celgene has inked 19 option-based agreements with early, mostly private-stage biotechs, securing access to what it believes are some of tomorrow's most promising oncology and immunology assets. In addition to its alliances with OncoMed Pharmaceuticals and Acetylon Pharmaceuticals, other notable deals have included its four other option-to-acquire transactions (VentiRx Pharmaceuticals, Quanticel Pharmaceuticals, PharmAkea Therapeutics and Forma Therapeutics) and its broad-based partnerships with Agios Pharmaceuticals and Epizyme.

While the specifics of each deal are different, Celgene's alliances are of a type: in exchange for sizeable up-front cash, Celgene has received options to many novel programs and in 10 instances, equity. Although these partnerships require the commitment of substantial capital, Celgene argues these deals enhance its pipeline optionality, allowing the big biotech to lock in rights to products at an early – and more cost-effective – development stage.

Creating optionality

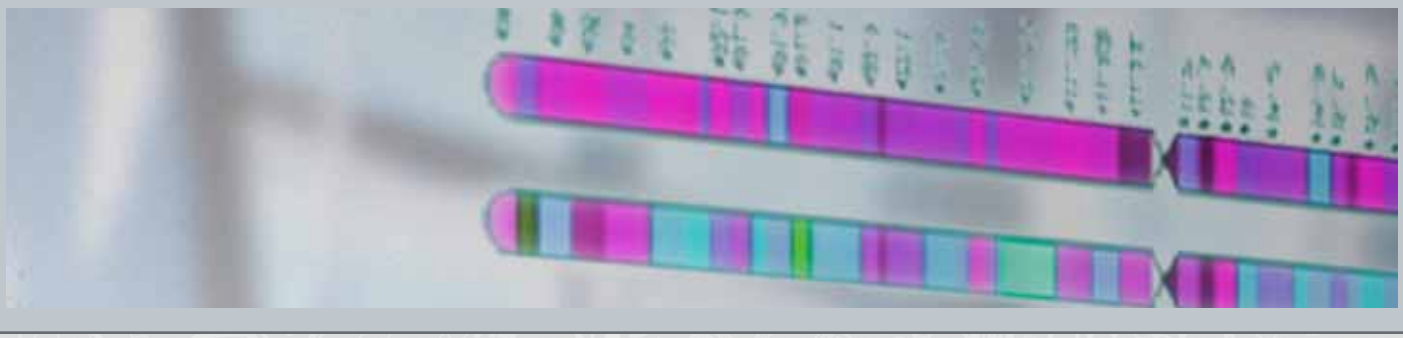
These deals have provided Celgene's biotech partners with considerable optionality, too. For starters, the biotechs retain control of their assets until any options are exercised, ensuring they can continue to develop the compounds via mechanisms that are most likely to add value. Moreover, these option deals often include significant development milestones and commercial rights, allowing the biotechs to realize additional value as their partnerships progress. Finally, the up-front cash should not be underestimated: it provides a lengthy financing runway – a luxury in the post-financial crisis era – freeing management teams from short-term fund-raising distractions to focus on building the next generation of independent biotechs.

And many of Celgene's partners are well on their way to achieving this goal. Of the 41 biotechs that completed IPOs in the US in 2013, five had existing partnerships with Celgene and one, OncoMed Pharmaceuticals, inked an alliance shortly after going public. (Concert Pharmaceuticals, which went public in early 2014, also has an alliance with the big biotech.) As a group, these start-ups have all continued to return money to their investors: share prices of the six companies were up 68% from their list prices by 30 April 2014, compared with 48% for the 2013 class as a whole.

Returns on equity

This strong aftermarket performance hasn't just benefited Celgene's biotech partners. The big biotech has benefited as well, thanks to the equity stakes it holds in five of them: Acceleron, PTC Therapeutics, Epizyme, OncoMed Pharmaceuticals and Agios Pharmaceuticals. Based on EY's estimates, Celgene paid its six biotech partners nearly US$ 600 million (in up-front payments and equity). Based on post-IPO market performance, Celgene's equity is now worth at least an estimated US$ 240 million. Had Celgene liquidated on 1 June 2014 the shares it had acquired at the time of its partners' public offerings – or in the case of OncoMed, the alliance's signing – it would have reaped a sevenfold return on its equity spend. It would also have recouped 40% of the total it spent on up-front payments.

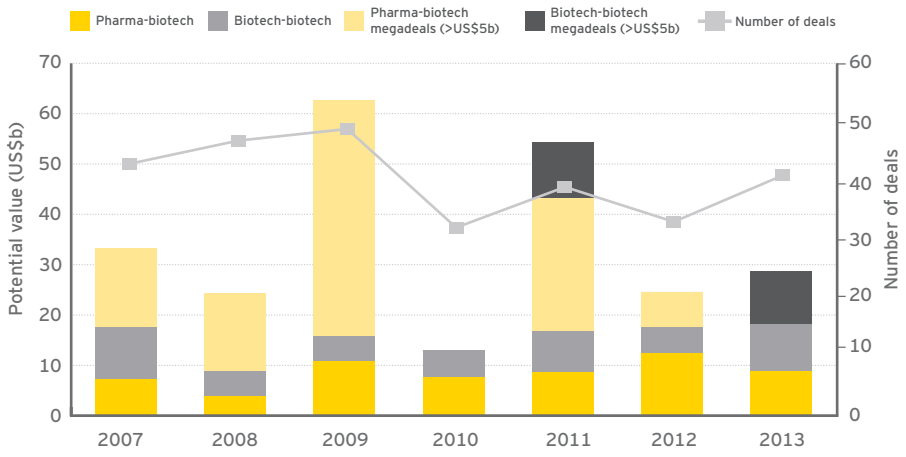
Of course, Celgene has shown no signs of exiting its ownership positions in any of its partners, and has even doubled down in three cases, buying additional shares of Acceleron, Agios Pharmaceuticals and Epizyme in the aftermarket. Celgene's continued support ensures its biotech partners are sufficiently capitalized to weather the vagaries of the public markets as well as the scientific ups and downs that go hand-in-hand with biotech R&D. As data emerge about the potential financial benefit to Celgene from such deals, it may spark other big biotech and pharma partners to re-examine a deal structure many considered too risky – and too expensive.



United States

In the US, total deal value rose 16% over 2012, to US$ 28.6 billion, and the number of deals jumped from 34 to 41, the highest total since 2009. Excluding the Amgen/Onyx Pharmaceuticals megadeal in 2013 and BMS/Amylin in 2012, deal value increased just 3% to US$ 18.2 billion year-over-year. Although transaction volume stayed relatively constant, biotech-biotech deal values nearly doubled from 2012 to 2013 thanks largely to acquisitions by Shire (ViroPharma), Cubist Pharmaceuticals (Trius Therapeutics and Optimer Pharmaceuticals) and The Medicines Company (Rempex Pharmaceuticals).

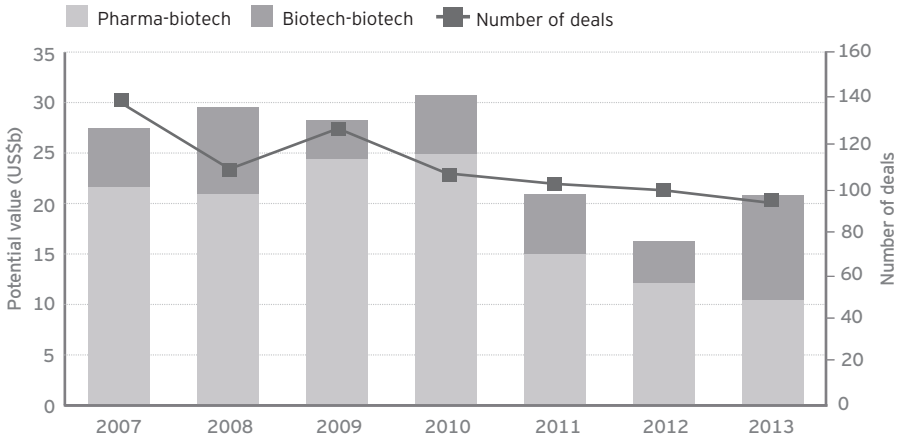
US M&As, 2007-13



Source: EY, Capital IQ, MedTRACK and company news.
Chart excludes transactions where deal terms were not publicly disclosed. Chart also excludes the 2013 Thermo Fisher/Life Technologies (US$ 13.6b) transaction because the acquirer is neither a pharma nor a biotech.

Biotech-biotech deals dominated the US alliance picture in 2013. Total alliance value increased 28% year-over-year in 2013, largely because of a big uptick in the value of biotech-biotech alliances. Meanwhile, for the third year in a row, the potential deal value for alliances between pharmas and US biotechs declined. Astellas Pharma and AstraZeneca were among the most active pharma alliance deal makers, each signing three deals with disclosed terms worth approximately up to US$ 1.5 billion.

US strategic alliances based on biobucks, 2007-13

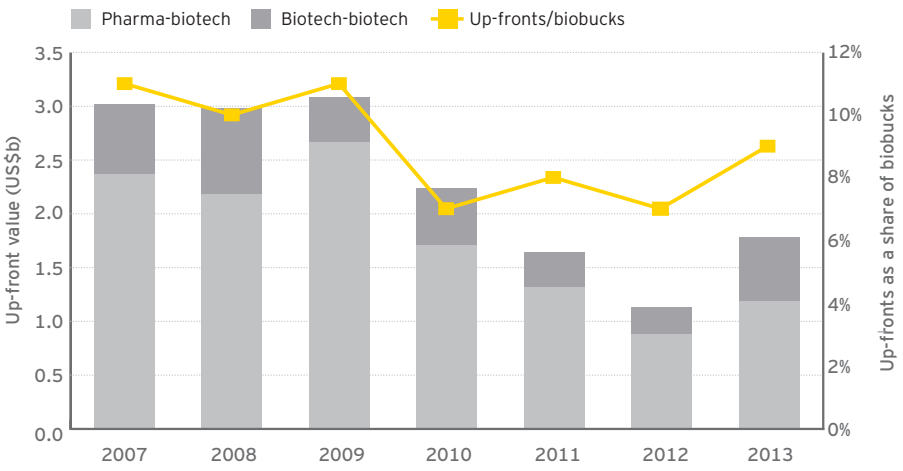


Source: EY, MedTRACK and company news.
Chart shows potential value, including up-front and milestone payments, for alliances where deal terms are publicly disclosed.

In 2013, US biotechs pulled in US$ 1.8 billion in up-front payments, a 50% increase from 2012. While the total up-front dollars generated in 2013 were roughly half what biotechs received in 2008 and 2009, the 2013 figures suggest a turnaround could be in the offing. Importantly, the ratio of up-fronts to biobucks returned to a healthier 9%, suggesting that as the capital markets have strengthened and competition for assets has increased, biotechs are able to negotiate that more value be recognized at the time of the deal's signing.

Biotech-biotech deals were a big contributor to the increase in up-fronts, generating US$ 600 million. Again, Celgene led the charge with its OncoMed Pharmaceuticals and Acetylon Pharmaceuticals alliances. Pharma-biotech up-front payments were also up from 2012, a 33% year-on-year gain to US$ 1.2 billion. That figure was, however, well below the 2009 high of US$ 2.7 billion.

US strategic alliances based on up-front payments, 2007-13



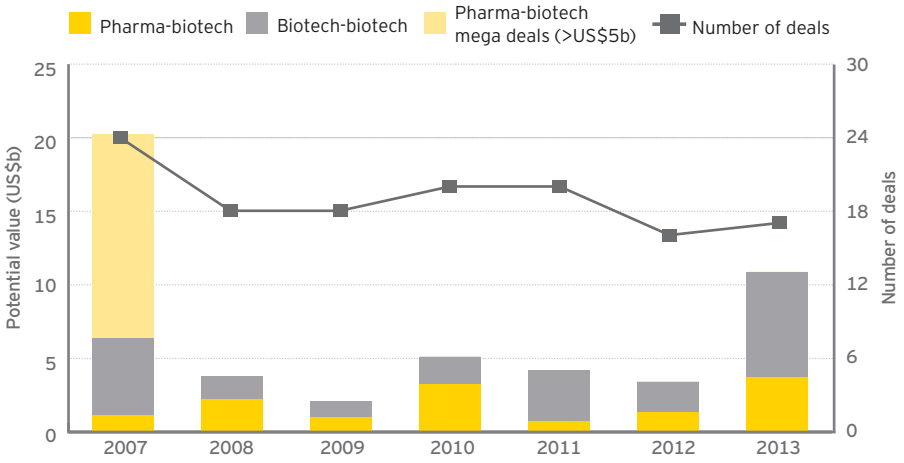
Source: EY, MedTRACK and company news.
Chart excludes transactions where deal terms were not publicly disclosed.

Europe

European deal makers enjoyed a bumper 2013 – the best year for M&A since 2007. The total value of the 21 European M&A deals in 2013 was US$ 19.6 billion, up 487% year-on-year and more than the previous five years rolled together.

2013 included one megadeal, US-based OTC manufacturer Perrigo's US$ 8.6 billion takeover of Ireland's Elan (excluded from the chart). This was the first European megadeal since Merck KGaA's acquisition of Serono for US$ 13.8 billion in 2007. Even without the Perrigo/Elan deal, the 2013 M&A tally would have reached US$ 11 billion, an increase of more than 200% on 2012. Biotech-biotech deal making drove the overall increase in deal value, but there was no dominant acquirer in the mix. The largest biotech-biotech deal, Jazz Pharmaceuticals' US$ 1 billion purchase of the Italian biotech Gentium, comprised roughly 14% of the total biotech-biotech acquisition dollars.

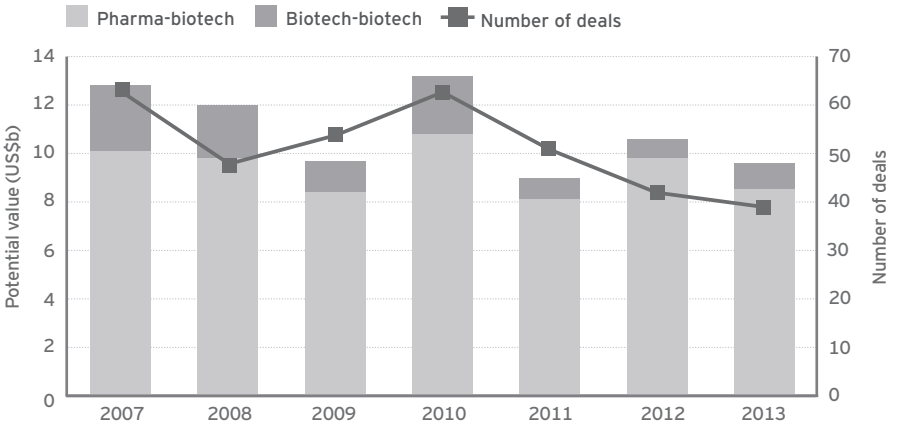
European M&As, 2007-13



Source: EY, Capital IQ, MedTRACK and company news.
Chart excludes transactions where deal terms were not publicly disclosed. Chart excludes Perrigo/Elan transaction (US$ 8.6b) because Perrigo is neither a pharma nor a biotech acquirer

M&A may have been on the ascendant in 2013, but European alliances were treading water as deal volume and total biobucks dipped slightly. The decline in biobucks resulted from pharma's retreat: alliances between pharmaceutical companies and European biotechs fell 13% to US$ 8.5 billion. In contrast, biotech-biotech alliances were up nearly 40% in 2013 to US$ 1.1 billion, which was the highest total since 2010. Even though biotech licensers took advantage of the vacuum created when pharmas trimmed their alliance activity, deal values in the class haven't returned to pre-European debt-crisis levels. Indeed, they remain a fraction of what US-based companies reaped in 2013. The picture is even less rosy when one considers that the Celgene/MorphoSys tie-up generated 78% of the total biotech-biotech deal value for the year.

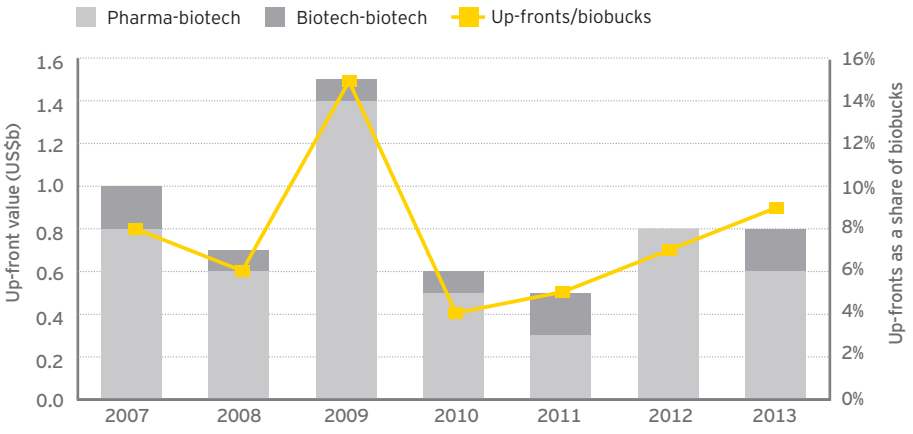
European strategic alliances based on biobucks, 2007-13



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

European up-front payments totaled US$ 800 million in 2013, which represented 9% of the total European deal value. As in the US, European companies that were able to sign deals in 2013 obtained more value up front than at any time since 2009. In addition to the Celgene/MorphoSys deal, other transactions with notable up-fronts included AbbVie/Ablynx (US$ 175 million), Roche/Chiasma (US$ 65 million) and Roche/Molecular Partners (US$ 59.4 million).

European strategic alliances based on up-front payments, 2007-13



Source: EY, MedTRACK and company news.
Chart shows up-front payments where deal terms are publicly disclosed.

Products and pipeline

Seeking novelty

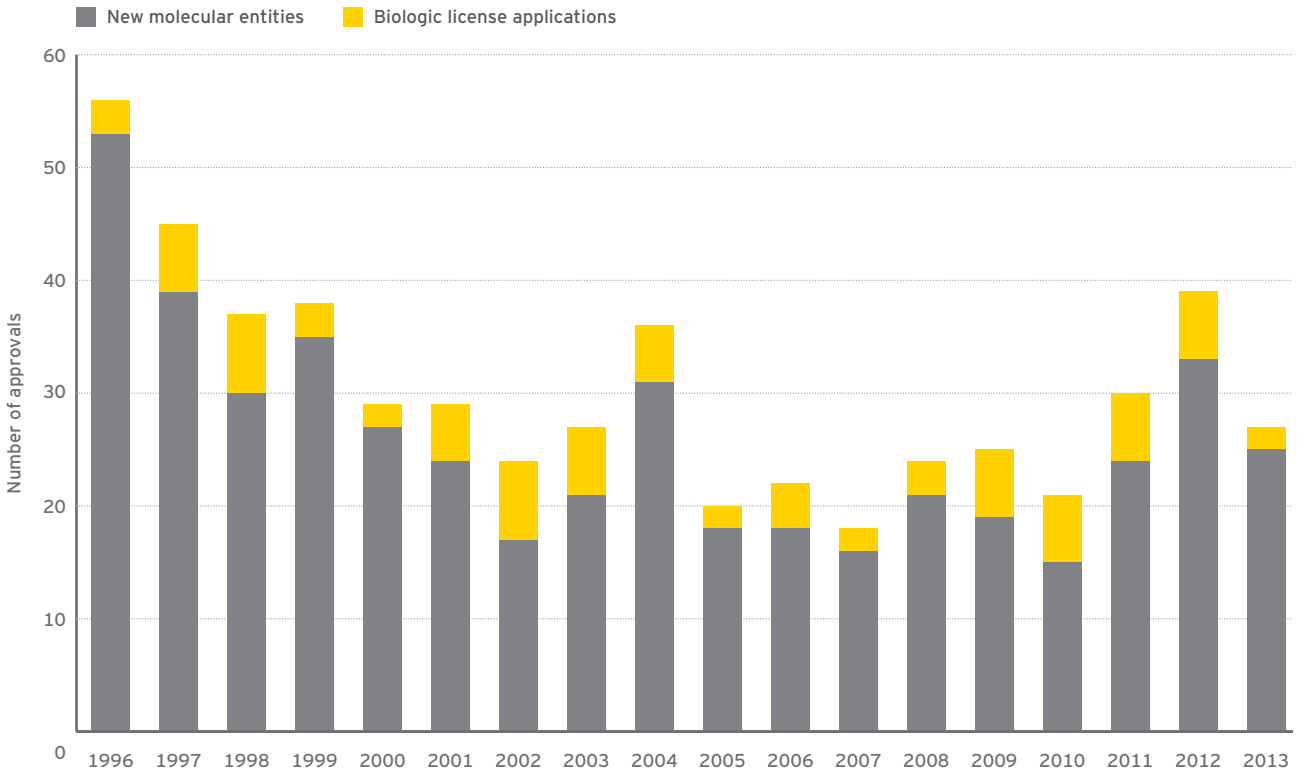
The big picture

In our 2013 report, we cheered what appeared to be the start of a more sustained upward trend in the number of new products approved as 2012 US FDA approvals reached levels not seen since 1997. That trend wasn't sustainable, and in 2013, only 27 new products were approved. As in 2012, first-in-class products, products with novel mechanisms of action and products for orphan indications were well represented in the 2013 class of new molecular entities.

In part, this is because companies are recognizing new therapies must demonstrate value to succeed with payers and in the marketplace. The good news is regulators are keen to prove they will support novel treatments in areas of high unmet medical need. In 2013, the FDA refined its process for expediting drug reviews and approvals adding the Breakthrough Therapy Designation program; in March 2014 the EMA launched a pilot program to allow certain medicines to utilize a staggered approval process that authorizes the earlier use of medicines but only in restricted patient populations. (Based on further evidence collection, the drug's use could be expanded to a broader patient population at a future date.)

It isn't necessarily the case that the ebb and flow of the market has little impact on biopharma drug development. Improved market conditions in 2013 helped to create the most favorable investment climate in over a decade, and biotech's commercial leaders responded by reinvesting in their R&D pipelines. Given the complexity of human disease and the capriciousness of drug discovery, all biopharma companies must continue to use tactics that enable them to create more value from their R&D efforts. As our opening "Point of view" explains, strategies such as adaptive clinical trials and biomarker approaches allow companies to perform smarter, more cost-effective R&D while simultaneously collecting evidence important to regulators and payers.

FDA product approvals, 1996–2013



Source: EY and FDA.
US product approvals are based on CDER approvals only.

A three-year upward trajectory in the number of approved new drug applications (NDAs) and biologic license applications (BLAs) came to a halt in 2013. The FDA approved 25 NDAs, down from 33 in 2012, and just two BLAs, down from six. That said, the 2013 figures were in line with the average number of approvals from 2004 to 2012. Meanwhile, the number of new applications dropped from 41 to 36 in 2013, which is consistent with the historical number of submissions.

Of the newly approved products, many are on their way to blockbuster status, including Biogen Idec's Tecfidera, an oral therapy for relapsing forms of multiple sclerosis, and Gilead Sciences' Sovaldi, an interferon-free oral treatment option for hepatitis C. Sovaldi, which was approved in late 2013, generated revenue in excess of US$ 2 billion in its first quarter on the market in 2014, partly because physicians were so excited about the drug's upcoming launch they refrained from putting new patients on existing therapies.

In addition to Sovaldi and Tecfidera, noteworthy new products developed by biotechs included Imbruvica (developed by Pharmacyclics and partnered with Johnson & Johnson), Actelion's Opsumit and Celgene's multiple myeloma therapy Pomalyst.

Nine of the 27 new products were first-in-class; another nine are treatments for orphan indications. In addition, three products – Imbruvica, Sovaldi and Roche's Kadcyla – were approved via the FDA's new Breakthrough Therapy expedited review process. In all, more than 50% of the drugs approved in 2013 took advantage of one of the FDA's expedited review processes. (See "New expedited regulatory pathways speed products to market," on page 30.) Meanwhile, the Center for Drug Evaluation and Research (CDER) met its PDUFA goal dates for 100% of the NMEs approved in 2013.

Based on the FDA's novel new drugs summary, GlaxoSmithKline topped the table for most new drugs approved – five in all, including the approval of its metastatic melanoma therapies Mekinist and Tafinlar and Viiv Healthcare's HIV treatment Tivicay. GlaxoSmithKline also won approval for its COPD treatment Breo Ellipta, which it developed in conjunction with Theravance. Biotech partners played important roles in the creation of other big pharma drugs approved in 2013: the cancer drug Kadcyla utilized key technology from Immunogen, and Algeta played such a pivotal role in the development of Xofigo that Bayer HealthCare bought out its smaller partner to get full rights to the prostate cancer medicine.

Cancer treatments accounted for eight of the 2013 approvals, including the only two biologics on the list – Roche's Gayza and Kadcyla. It was also a big year for infectious disease products, most notably drugs for hepatitis C: the aforementioned Sovaldi and Johnson & Johnson's Olysio.

Selected orphan drug approvals by the FDA, 2013

Company	Brand name	Generic name	Type of approval	Indication	Review classification	Month
Sanofi	Kynamro	Mipomersen sodium	New molecular entity	Homozygous familial hypercholesterolemia	Standard	January
Celgene	Pomalyst	Pomalidomide	New molecular entity	Multiple myeloma	Standard	February
GlaxoSmithKline	Mekinist	Trametinib	New molecular entity	Metastatic melanoma	Standard	May
GlaxoSmithKline	Tafinlar	Dabrafenib	New molecular entity	Metastatic melanoma	Standard	May
Boehringer Ingelheim	Gilotrif/Giotrif	Afatinib	New molecular entity	Metastatic non-small cell lung cancer	Priority	July
Bayer HealthCare	Adempas	Riociguat	New molecular entity	Pulmonary hypertension	Priority	October
Actelion	Opsumit	Macitentan	New molecular entity	Pulmonary arterial hypertension	Standard	October
Roche	Gazyva	Obinutuzumab	New biologic license application	Chronic lymphocytic leukemia	Priority	November
Johnson & Johnson	Imbruvica	Ibrutinib	New molecular entity	Mantle cell lymphoma	Priority	November

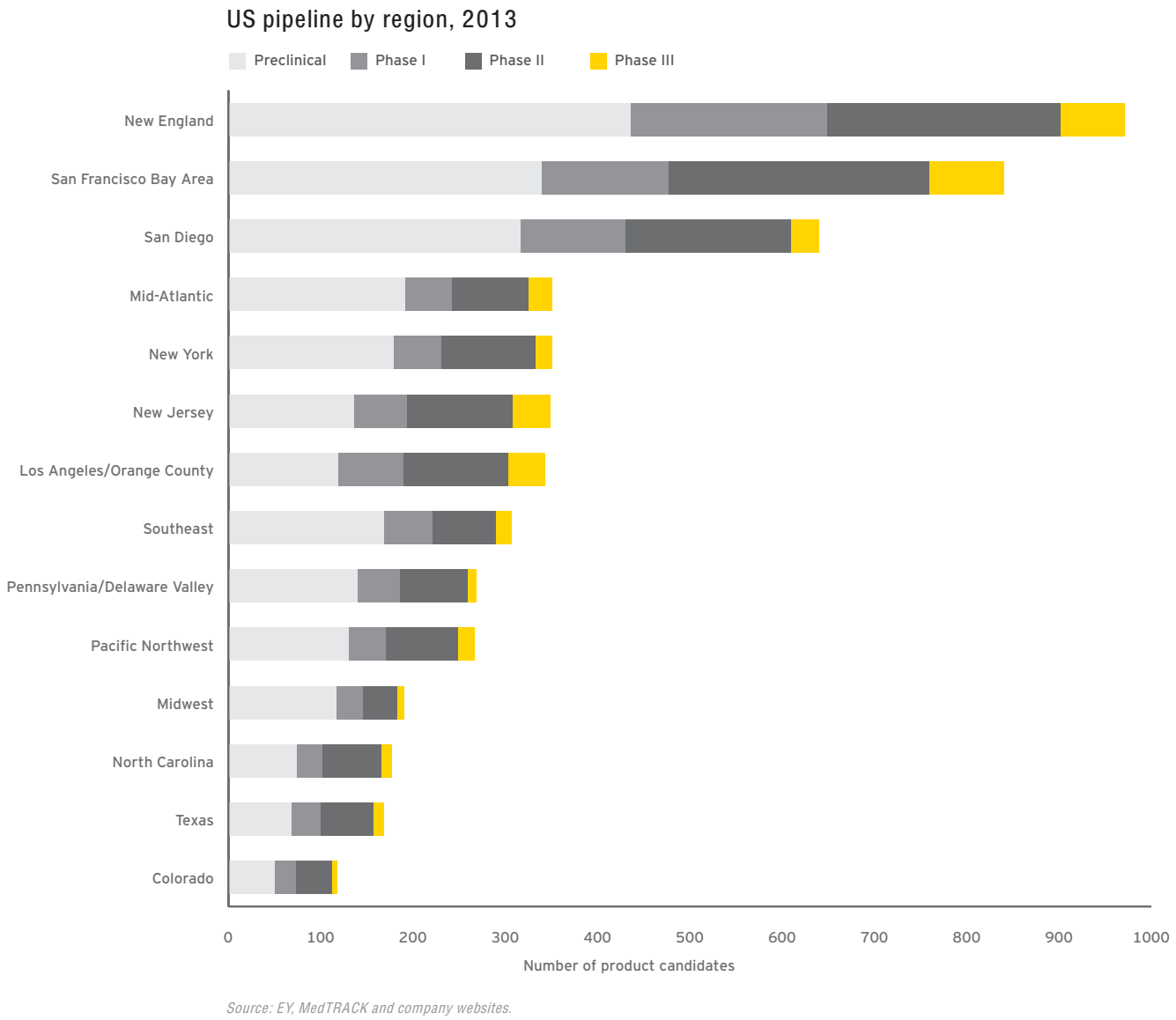
Source: EY, FDA and company websites.

Other selected FDA approvals, 2013

Company	Brand name	Generic name	Type of approval	Indication	Month
Takeda Pharmaceutical Co.	Nesina	Alogliptin	New molecular entity	Type 2 diabetes	January
Roche	Kadcyla	Ado-trastuzumab emtansine	New biologic license application	Metastatic breast cancer	February
Shionogi	Osphena	Ospemifene	New molecular entity	Severe dyspareunia	February
Biogen Idec	Tecfidera	Dimethyl fumarate	New molecular entity	Multiple sclerosis	March
Johnson & Johnson	Invokana	Canagliflozin	New molecular entity	Type 2 diabetes	March
GlaxoSmithKline	Breo Ellipta	Fluticasone furoate and vilanterol	New molecular entity	Chronic obstructive pulmonary disease	May
Bayer HealthCare	Xofigo	Radium dichloride	New molecular entity	Metastatic castration-resistant prostate cancer	May
Viiv Healthcare	Tivicay	Dolutegravir	New molecular entity	Human immunodeficiency virus-1	August
Takeda Pharmaceutical Co.	Brintellix	Vortioxetine	New molecular entity	Depression	September
Pfizer	Duavee	Conjugated estrogens/ bazedoxifene	New molecular entity	Menopausal hot flashes and osteoporosis prevention	October
Sunovion	Aptiom	Eslicarbazepine acetate	New molecular entity	Epilepsy	November
Medicis	Luzu	Luliconozole	New molecular entity	Interdigital tinea pedis, tinea cruris and tinea corporis	November
Johnson & Johnson	Olysio	Simeprevir	New molecular entity	Chronic hepatitis C virus	November
Gilead Sciences	Sovaldi	Sofosbuvir	New molecular entity	Chronic hepatitis C virus	December
GlaxoSmithKline	Anoro Ellipta	Umeclidinium and vilanterol	New molecular entity	Chronic obstructive pulmonary disease	December

Source: EY, FDA and company websites.

United States

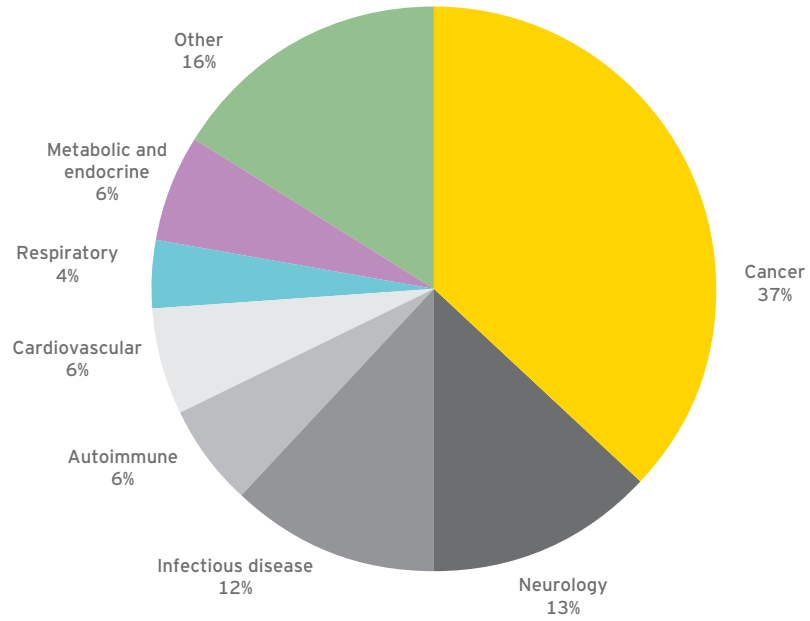


Source: EY, MedTRACK and company websites.

Overall, the drug pipeline for US publicly traded biotech companies increased by 9% in 2013, with 5,634 products now under development. The top three regions were New England, whose companies are now responsible for 17% of drugs in the biopharmaceutical pipeline, the San Francisco Bay area (15%) and San Diego (11%).

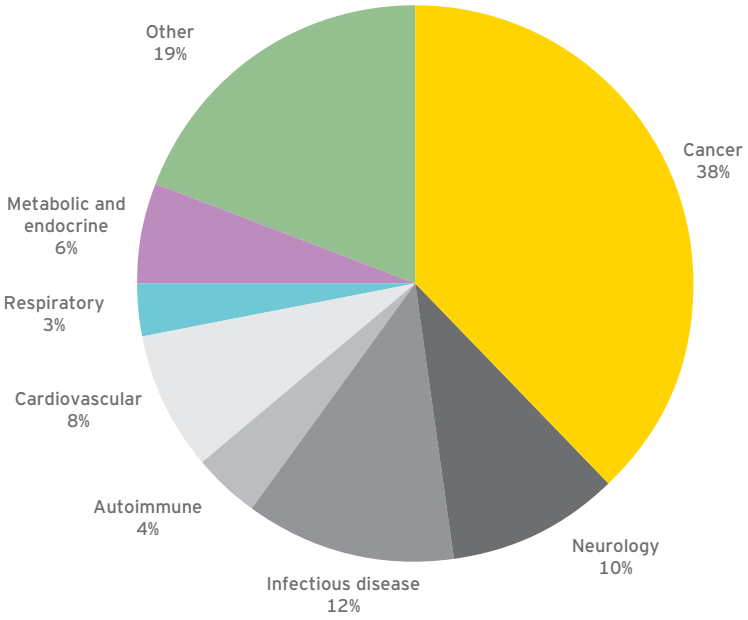
Oncology drugs continued to dominate US pipelines in 2013, making up 37% of all compounds under development and 38% of the Phase III pipeline. But that was down from 43% in 2012, as the number of drugs to treat infectious disease and autoimmune diseases increased.

US pipeline by indication, 2013



Source: EY, MedTRACK and company websites.

US Phase III pipeline by indication, 2013



Source: EY, MedTRACK and company websites.

Europe

Orphan drug approvals by the EMA, 2013

Company	Brand name	Generic name	Indication	Month
Pfizer	Bosulif	Bosutinib	Chronic myelogenous leukemia	January
ARIAD Pharmaceuticals	Iclusig	Ponatinib	Chronic myeloid leukemia or lymphoblastic leukemia	March
Celgene	Imnovid	Pomalidomide	Multiple myeloma	May
Raptor Pharmaceuticals	Procysbi	Mercaptamine	Cystinosis	June
Gentium	Defitelio	Defibrotide	Hepatic veno-occlusive disease	July
FGK Representative Service	Cholic acid fgk	Cholic acid	Inborn errors of primary bile acid synthesis	November
Lucane Pharma	Paser	Aminosalicylic acid	Multi-drug resistant tuberculosis	November
TMC Pharma Services	Cometriq	Cabozantinib	Medullary thyroid carcinoma	December
Actelion	Opsumit	Macitentan	Pulmonary arterial hypertension	December
Johnson & Johnson	Sirturo	Bedaquiline	Multi-drug resistant tuberculosis	December
Otsuka	Deltyba	Delamanid	Multi-drug resistant tuberculosis	December

Source: EY, EMA and company websites.

Other selected EMA approvals, 2013

Company	Brand name	Generic name	Indication	Month
Sanofi	Hexacima/Hexyon	Conjugate vaccine	Haemophilus influenzae type B	February
Baxter	Hyqvia	Human normal immuno-globulin	Immunodeficiency syndrome	March
Gilead Sciences	Stribild	Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil	Human immunodeficiency virus-1	March
Biogen Idec	Tecfidera	Dimethyl fumarate	Multiple sclerosis	March
Roche	Erivedge	Vismodegib	Advanced basal cell carcinoma	April
Menarini	Spedra	Avanafil	Erectile dysfunction	April
Astellas Pharma	Xtandi	Enzalutamide	Prostate cancer	April
Bayer HealthCare	Stivarga	Regorafenib	Metastatic colorectal cancer	June
GlaxoSmithKline	Tafinlar	Dabrafenib	Metastatic melanoma	June
Boehringer Ingelheim	Gilotrif/Giotrif	Afatinib	Metastatic non-small cell lung cancer	July
Takeda Pharmaceutical Co.	Vipidia	Alogliptin	Type 2 diabetes	July
Johnson & Johnson	Invokana	Canagliflozin	Type 2 diabetes	September
Roche	Kadcyla	Trastuzumab emtansine	Metastatic breast cancer	September
GlaxoSmithKline	Relvar ellipta	Fluticasone furoate/vilanterol	Asthma and COPD	September
Bayer HealthCare	Xofigo	Radium-223	Castration-resistant prostate cancer	September
Gilead Sciences	Sovaldi	Sofosbuvir	Chronic hepatitis C virus	November

Source: EY, EMA and company websites.

The European Medicines Agency (EMA) recommended 81 drugs for marketing authorization in 2013, of which 38 were NMEs and 20 were generics. The number of NMEs approved by the EMA has steadily increased in recent years: in 2010, there were 15, in 2011, there were 25, and in 2012, there were 35.

The number of marketing-authorization applications (MAA) to the EMA has remained at a steady level for many years. However, the agency has noted a marked increase in the complexity of applications, including a growing number of MAAs for orphan drugs. Because of the additional intricacies, 50% of applicants sought additional scientific advice from the EMA's Committee for Medicinal Products for Human Use (CHMP) before submitting their applications. Such dialogue may have contributed to the high number of approved NMEs in 2013. The EMA pointed out there was a 90% recommendation success rate for companies that obtained and complied with CHMP's advice.

Noteworthy European recommendations included approvals for the first two monoclonal antibody biosimilar drugs, Remsima (from Hungary's Celltrion Healthcare) and Inflectra (from US' Hospira). Both contain the same known active substance, infliximab, and are similar to Remicade, a monoclonal antibody that has been authorized in the European Union since 1999.

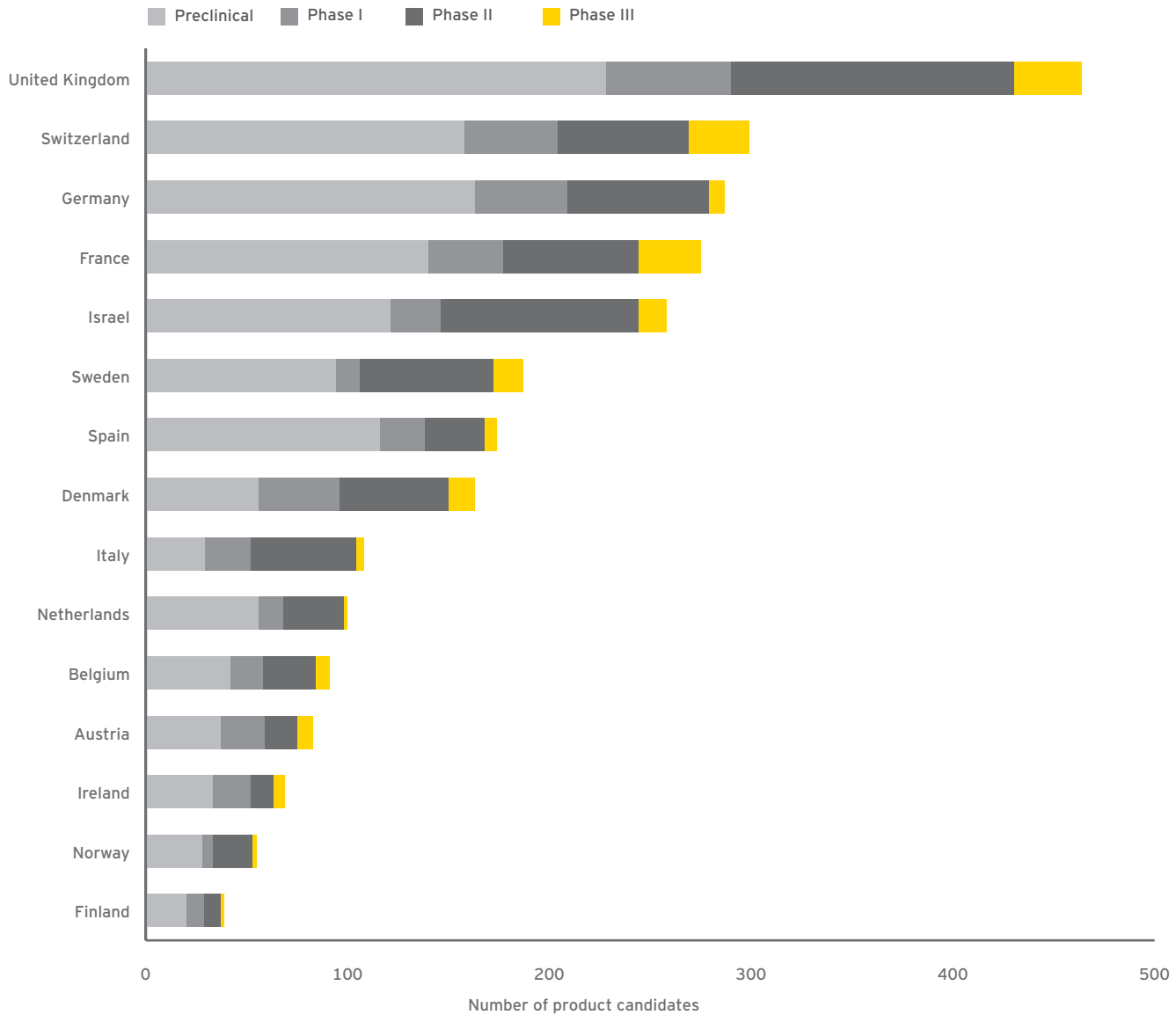
In 2013, the EMA also recommended two new advanced-therapy medicinal products (ATMPs), which are products derived from gene therapy, cell therapy or tissue engineering: Dendreon's Provenge for treatment of metastatic prostate cancer and Sanofi's MACI (matrix-induced autologous cultured chondrocytes) for repair of cartilage defects.

The EMA recommended 11 orphan drugs in 2013, up from eight in 2012 and four in 2011. Three of the 11 were for the treatment of multi-drug resistant tuberculosis, an orphan indication associated with a very high mortality rate given the absence of new treatment options. The EMA also followed the FDA's lead in recommending the potential blockbusters Sovaldi, Kadcyla and Tecfidera for authorization in Europe.

Including Kadcyla, 16 drugs were approved for cancer, four for HIV (all were new active substances) and five for Type 2 diabetes (four were new active substances). Two new treatments were approved for prostate cancer: Astellas Pharma's androgen receptor signaling inhibitor enzalutamide and Bayer HealthCare's radiotherapeutic drug radium-223.

Although around 40% of the European-sourced drugs in clinical trials are oncologics, only 19% of the medicines EMA approved in 2013 fell into this category. The divergence illustrates yet again how challenging oncology drug development can be.

European pipeline by country, 2013

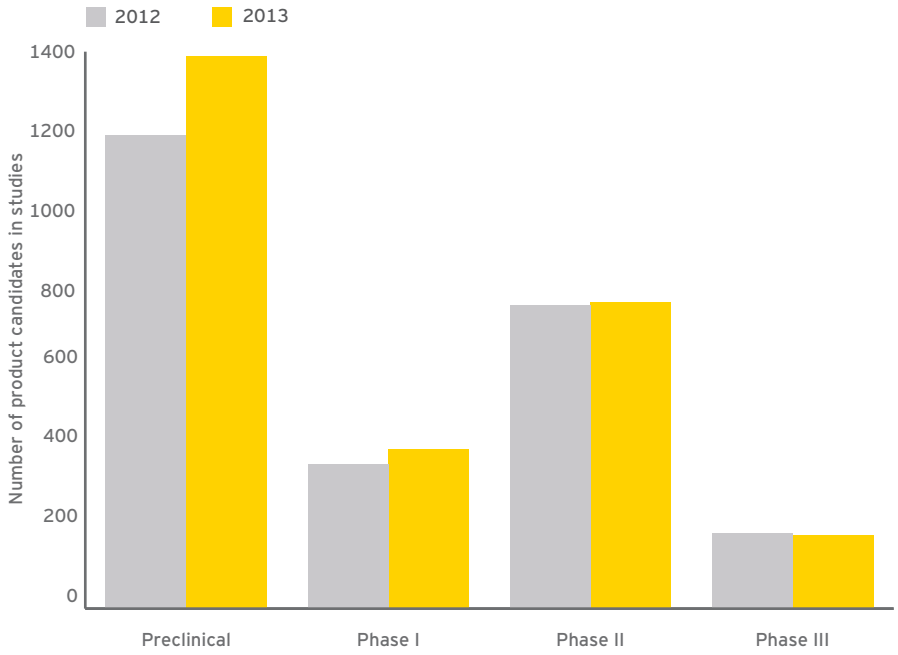


Source: EY, MedTRACK and company websites.

The European drug pipeline grew by 10% in 2013, with a total of 2,743 products, still less than half the size of the US' drug pipeline. The growth was largely driven by activity in preclinical and Phase I development. The number of preclinical candidates increased 17% to nearly 1,400 candidates, while the number of Phase I contenders grew 10%. Products in Phase III declined 3% to 184 candidates.

The UK remained the pipeline leader, with 464 products, or 17% of the total, ahead of Switzerland (299) and Germany (287). Together, the UK, Switzerland, Germany, France and Israel contributed nearly 60% of the total European pipeline. The UK was home to 34 Phase III drug candidates in 2013, ahead of France (31) and Switzerland (30).

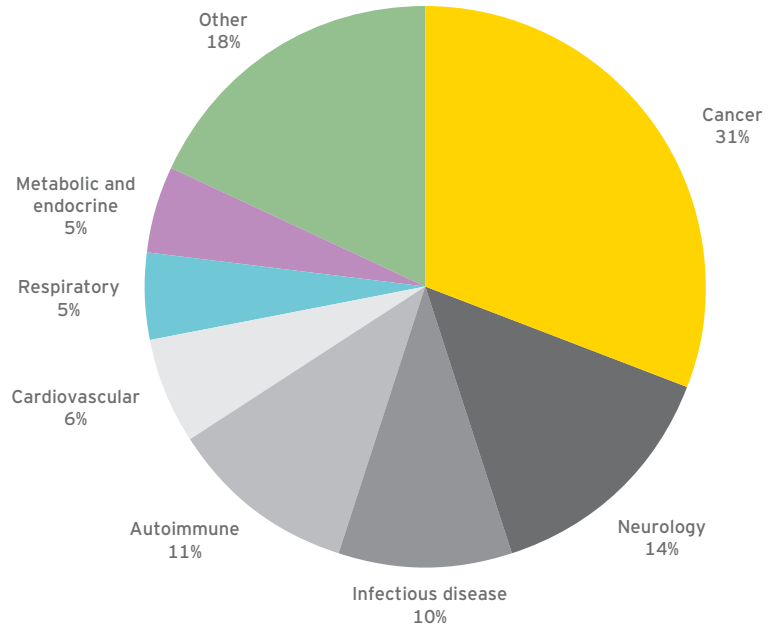
European pipeline by year



Source: EY, MedTRACK and company websites.

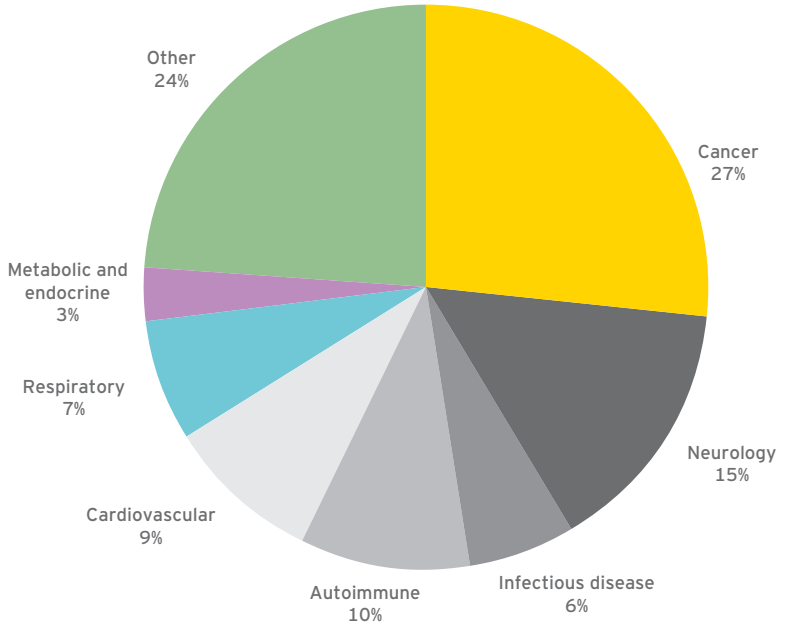
As in the US, oncology drugs dominated European therapeutic pipelines in 2013, with 31% of the total. Treatments for autoimmune diseases were up slightly at 11%.

European pipeline by indication, 2013

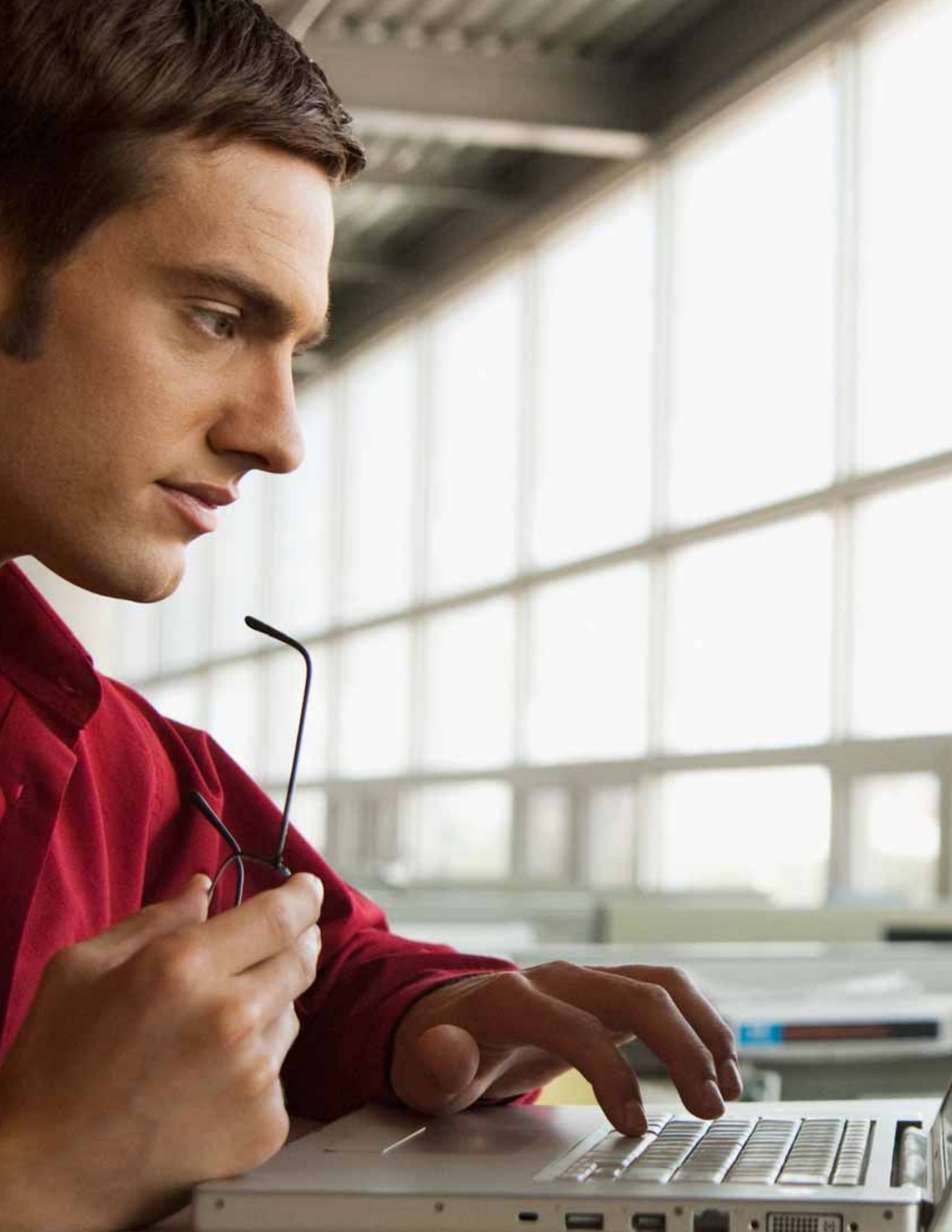


Source: EY, MedTRACK and company websites.

European Phase III pipeline by indication, 2013



Source: EY, MedTRACK and company websites.
Numbers may appear inconsistent due to rounding.



Acknowledgments

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

Gautam Jaggi, was the overall Editor of the publication. He helped develop key themes of the report, contributed to the "Point of view" and "Financial performance" articles and provided important insights into industry trends. Gautam also helped guide the design of the report.

Ellen Licking, Contributing Writer, and **Iain Scott,** Analyst in EY's Global Life Sciences Center, were the report's lead authors. Ellen wrote the "Point of view" article and added substantial content to the "Financing" and "Deals" articles, working closely with Gautam, Glen and Iain. Iain was the lead writer for the remaining articles. Ellen and Iain also conducted most of the interviews for the report and drafted the guest articles.

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Kraig Schulz and **Sarah Bobulsky** developed the financial model to demonstrate the impact of adaptive clinical trials.

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Data exhibit index

Global biotechnology contacts

Global Life Sciences Leader		Glen Giovannetti	glen.giovannetti@ey.com	+1 617 374 6218
Deputy Global Life Sciences Leader and Global Pharmaceutical Leader		Patrick Flochel	patrick.flochel@ch.ey.com	+41 58 286 4148
Global Life Sciences Assurance Leader		Scott Bruns	scott.bruns@ey.com	+1 317 681 7229
Global Life Sciences Advisory Leader		Kim Ramko	kim.ramko@ey.com	+1 615 252 8249
Global Life Sciences Tax Leader		Mitch Cohen	mitchell.cohen@ey.com	+1 203 674 3244
Global Life Sciences Transaction Advisory Services Leader		Jeff Greene	jeffrey.greene@ey.com	+1 212 773 6500
Global Life Sciences Lead Analyst and Managing Editor		Gautam Jaggi	gautam.jaggi@ey.com	+1 617 374 6315
Australia	Brisbane	Winna Brown	winna.brown@au.ey.com	+61 7 3011 3343
	Melbourne	Denise Brotherton	denise.brotherton@au.ey.com	+61 3 9288 8758
	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
Belgium	Brussels	Dick Hoogenberg	dick.hoogenberg@nl.ey.com	+31 88 40 71419
Brazil	São Paulo	Frank de Meijer	frank-de.meijer@br.ey.com	+55 11 2573 3383
Canada	Montréal	Sylvain Boucher	sylvain.boucher@ca.ey.com	+1 514 874 4393
		Lara Iob	lara.iob@ca.ey.com	+1 514 879 6514
	Toronto	Mario Piccinin	mario.piccinin@ca.ey.com	+1 416 932 6231
	Vancouver	Nicole Poirier	nicole.poirier@ca.ey.com	+1 604 891 8342
Czech Republic	Prague	Petr Knap	petr.knap@cz.ey.com	+420 225 335 582
Denmark	Copenhagen	Staffan Folin	staffan.folin@se.ey.com	+46 8 5205 9359
Finland	Helsinki	Timo Virkilä	timo.virkila@fi.ey.com	+358 207 280 190
France	Lyon	Virginie Lefebvre-Dutilleul	virginie.lefebvre-dutilleul@ey-avocats.com	+33 1 55 61 10 62
	Paris	Franck Sebag	franck.sebag@fr.ey.com	+33 1 46 93 73 74
Germany	Düsseldorf	Gerd Stürz	gerd.w.stuerz@de.ey.com	+49 211 9352 18622
	Mannheim	Siegfried Bialojan	siegfried.bialojan@de.ey.com	+49 621 4208 11405
Greater China	Beijing	Jane Yang	jane-sj.yang@cn.ey.com	+86 10 5815 3331
	Shanghai	Felix Fei	felix.fei@cn.ey.com	+86 21 22282586
India	Mumbai	Hitesh Sharma	hitesh.sharma@in.ey.com	+91 22 6192 0950
		V. Krishnakumar	krishnakumar.v@in.ey.com	+91 22 6192 0950
Ireland	Dublin	Aidan Meagher	aidan.meagher@ie.ey.com	+353 1221 1139
Israel	Tel Aviv	Eyal Ben-Yaakov	eyal.benyaakov@il.ey.com	+972 3 623 2512
Italy	Milan	Gabriele Vanoli	gabriele.vanoli@it.ey.com	+39 02 8066 9840
	Rome	Alessandro Buccella	alessandro.buccella@it.ey.com	+39 06 67535630
		Antonio Irione	antonio.irione@it.ey.com	+39 06 6755715
Japan	Tokyo	Hironao Yazaki	yazaki-hrn@shinnihon.or.jp	+81 3 3503 2165
		Yuji Anzai	anzai-yj@shinnihon.or.jp	+81 3 3503 1100

Korea	Seoul	Jeungwook Lee	jeung-wook.lee@kr.ey.com	+82 2 3787 4301
Netherlands	Amsterdam	Jules Verhagen	jules.verhagen@nl.ey.com	+31 88 407 1888
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
Russia/CIS	Moscow	Dmitry Khalilov	Dmitry.Khalilov@ru.ey.com	+7 495 755 9757
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
Spain	Barcelona	Dr. Silvia Ondategui-Parra	silvia.ondateguiparra@es.ey.com	+34 93 366 3740
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	jlloydhirst@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
	Chicago	Jerry DeVault	jerry.devault@ey.com	+1 312 879 6518
	Dallas	Kenneth Bernstein	kenneth.bernstein@ey.com	+1 214 969 8903
	Houston	Carole Faig	carole.faig@ey.com	+1 713 750 1535
	Indianapolis	Andy Vrigian	andy.vrigian@ey.com	+1 317 681 7000
	Los Angeles	Don Ferrera	don.ferrera@ey.com	+1 213 977 7684
	New York/New Jersey	Tony Torrington	anthony.torrington@ey.com	+1 732 516 4681
		David De Marco	dave.demarco@ey.com	+1 732 516 4602
	Orange County	Kim Letch	kim.letch@ey.com	+1 949 437 0244
		Mark Montoya	mark.montoya@ey.com	+1 949 437 0388
	Philadelphia	Steve Simpson	stephen.simpson@ey.com	+1 215 448 5309
		Howard Brooks	howard.brooks@ey.com	+1 215 448 5115
	Raleigh	Mark Baxter	mark.baxter@ey.com	+1 919 981 2966
	Redwood Shores	Scott Morrison	scott.morrison@ey.com	+1 650 496 4688
		Chris Nolet	chris.nolet@ey.com	+1 650 802 4504
	San Diego	Dan Kleeburg	daniel.kleeburg@ey.com	+1 858 535 7209
	Seattle	Kathleen Smith	kathy.smith@ey.com	+1 206 654 6305
	Washington, D.C.	Rene Salas	rene.salas@ey.com	+1 703 747 0732

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