Weighing the outcomes

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The emergent healthcare value era, its consequences, and what drug firms need to do about it

In the United States, biologics have not historically received the rigorous pharmacoeconomic scrutiny to which managed care payers have systematically subjected small-molecule therapies beginning in 2002. But, with the total amount spent on specialty pharmaceuticals rising dramatically to over $54 billion, representing ~20% of the entire pharmaceutical bill and increasing at 20% per year on average, biologics have caught managed care payers' attention (**Fig. 1**).

Increasingly, payers are aggressively addressing the cost of biologics by rigorously assessing their overall healthcare value, incorporating components of clinical and economic worth. Payers are making decisions about coverage of and access to biologics within a framework that is heavily based on the strength of a biologic's healthcare value proposition—the relationship between the incremental health improvements it produces compared with its incremental cost, all relative to standard-of-care therapies. With biologics' high price tags (in the $10,000–500,000/year range) in mind, payers seek to allow only the most appropriate populations access to these drugs.

Likewise, payers have shifted the burden of proof to manufacturers, requiring that manufacturers provide clear evidence supporting their claims or face having those claims ignored. Most biotech and pharma companies are simply not prepared for such a shift because their focus has always been on satisfying the needs of patients and physicians, largely setting payers aside. But manufacturers must consider making structural and process-oriented changes, including to their research and development (R&D) organizations, if they are to remain competitive within the emerging marketplace.

Biologics are coming under increasing scrutiny by healthcare payers.

Outcomes-based access

Managed care payers have stepped up their efforts to control ever-increasing healthcare costs. These cost-control efforts have disproportionately focused on reigning in pharmaceutical expenditures, thus transforming the pharma landscape and fueling the rise of the multibillion dollar pharmacy-benefit management, specialty pharmacy and disease-management industries.

As little as a decade ago, health plans did not routinely incorporate what are now considered commonplace management tools, such as multi-tier formularies and ever-increasing copayments. These tools have been stepping stones—however riddled with growing pains—on a methodical and rather cohesive journey. The ultimate destination: collectively coalescing around a standardized approach, which elevates and centralizes the payer role within the decision-making and dispensing pathway for pharmaceutical and biological therapies, called outcomes-based access (OBA).

The OBA approach empowers payers to make coverage decisions on the basis of their determination of a drug's healthcare value—namely the degree to which a drug's impact on patient health and well-being addresses an outstanding clinical need at a price commensurate to the actual (that is, real-world) health outcomes it delivers. Payers then link formulary placement, drug coverage and access to their assessments of a drug's comparative healthcare value, incorporating improvements in clinical measures, quality of life and productivity (**Box 1**). Although most European and other developed countries have centralized healthcare value in their drug coverage and access decisions for years, until recently, rigorous economic analyses have not been incorporated into the standard for drug access in the United States.

Value, however, is a subjective concept, and what a particular stakeholder group values is based on its priorities. The fact is, coverage decisions now rest largely with payers, and therefore those benefits that accrue value to the insurance system (such as fewer surgeries, reduced visits to doctors, etc.) and its funders are most heavily weighted. It will be a challenge, but perhaps one worth taking on, for manufacturers and payer groups to expand this definition to include items that improve lives and enhance society, but do not accrue concrete value to the healthcare system.

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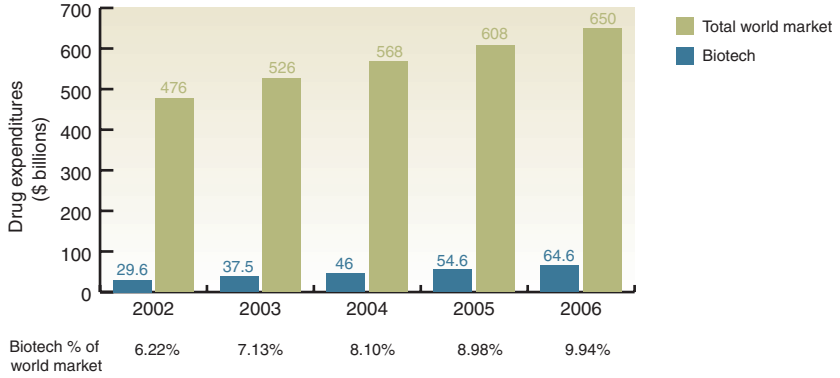

Figure 1 Growth in drug expenditures. The percent of drug expenditures attributable to biologics is increasing each year. Source: IMS Health, Norwalk, CT, USA.

OBA changes the effective payer 'default' for coverage decisions. In the past, payers usually covered new therapeutics unless there was a compelling reason otherwise. With OBA, payers increasingly maintain a restrictive default coverage and access status, unless the therapeutic's healthcare value proposition, with credible evidence, supports broader coverage. And the degree to which coverage is broadened is directly linked to the strength of the value proposition—again incorporating clinical and economic concerns (**Fig. 2**).

Although the initial managed care payer focus was primarily on small-molecule pharmaceuticals, our 2005 Payer Study measured a dramatic intensification of cost-control focus on biologics and other specialty pharmaceuticals. (We will use the broad umbrella term 'biologics' here, even though not all drugs covered under the specialty pharmacy rubric—expensive, typically injectible/infusible, difficult-to-manage drugs not often used in the primary care setting—are biologics.) The result is that biologics, which were in the past largely exempt from OBA by managed care payers, are now receiving the same degree of scrutiny as—and in many cases more scrutiny than—small-molecule therapies.

Jay McKnight, clinical pharmacist, pharmacy & therapeutics at Humana, has described Humana's approach, which few other major managed care payers diverge from. "We have our eye on specialty products in general, as we've seen our spend increase over the last several years." McKnight has also indicated that Humana is "using a cost-effectiveness model—are the additional outcomes worth the additional cost associated with the medication?" What's more, although in the past managed care payers made healthcare value exemptions for such diseases as cancer and HIV, our 2007 Payer Study clearly indicates that these disease areas are increasingly no longer off-limits and will become the focus of significant access and coverage restrictions in the coming years.

OBA presents real challenges, both to payers and other healthcare stakeholders. Many questions remain unanswered. What standards will be applied for therapeutic evaluation? Are the current tools adequate? How much information should be collected for evaluation? Whose responsibility is it to perform the necessary studies? How can such detailed information be collected before launch while the focus is on safety and efficacy within the very controlled clinical trial setting?

The bottom line: for a manufacturer, OBA means that from clinical trials through marketing, the payer perspective and healthcare value considerations must be centrally incorporated to ensure the development of a commercially viable therapeutic.

OBA and the development of new biologics

To understand why payers are applying OBA to biologics, consider the evolution that the biologics marketplace has experienced in the past ten years. Many of the first biologics to reach the market were for diseases with relatively small patient populations, such as Gaucher's disease, offering efficacious treatment options where none previously existed. They were expensive, but the total amount spent was relatively small and their mere existence was considered a technological revolution. Yet, over the years, expensive biological therapies have become available for diseases with much larger patient populations, such as rheumatoid arthritis, hepatitis C, multiple sclerosis and psoriasis. And with over 400 biological therapies in development, many targeting diseases with very large patient populations, such as cardiovascular and Alzheimer's disease, payers quickly realized they had no choice but to develop an understanding of how to appropriately gauge the healthcare value of biologics, manage their use and if necessary, tightly restrict access.

Some managed care companies are further along than others in independently assessing a new therapy's pharmacoeconomic and/or healthcare value and ensuring that its use is consistent with this determination. What is unmistakable, however, is that virtually all managed care payers have centralized OBA in their decision-making process, and all are creating or enhancing infrastructure and mechanisms for enforcement.

In the past, manufacturers saw their greatest revenue challenges, post-approval by the US Food and Drug Administration (FDA), in gaining physician acceptance of therapies and raising patient awareness. Reimbursement, on the other hand, has always been perceived as a much lower-level concern because, in the words of one Wall Street biotech analyst, "once a new therapy makes it to the market, payers don't really have any choice but to pay for it." If this is considered a truism, what happens when payers assert themselves as a primary customer, demanding that economic considerations be integrated into treatment selection?

The business models of pharmaceutical and biotech companies have been predicated on the belief that payers were at best an 'irritant' on the road to revenue generation. Payers are now leveraging their position as a central figure, able not only to set up access-control programs, but also to influence the behavior of both patients and physicians (**Box 2**). As a result, the primary challenge facing manufacturers after FDA approval is to ensure that their new therapies do not meet extreme access restrictions. At a minimum, new biologics need to present acceptable healthcare value propositions to payers; more optimally, they need to offer something compelling.

These shifts clearly provide opportunities for those pharmaceutical (**Box 3**) and biotech (**Box 4**) companies that evolve to incorporate the payer perspective into their business models and consistently create products with demonstrable healthcare value. In this regard, we are not saying that all new therapies must be revolutionary to gain acceptance and produce significant revenue, but rather that all therapies and especially those with incremental benefits, however important, should not be priced far in excess of their value.

Although payer assessments of healthcare value represent a new development hurdle for companies, it is far from an insurmountable one. With proper planning, companies can incorporate a variety of processes into their development efforts that will make it possible to address this payer need. In fact, we believe that companies should see this not simply as a

'compliance' issue to ensure that their products remain viable, but to see it more broadly—as an opportunity to build a sustainable competitive advantage that drives growth and distances competitors. We provide some guidance for reaching these goals later in this article.

Even so, in our experience as strategy consultants for executives at large and medium-sized pharmaceutical and biotech companies, we have found that most researchers and companies developing new biological therapies, if they have addressed these issues at all, have not done so in a meaningful way. Worse still, many do not fully understand how much the market has changed in this regard.

Wall Street is also taking notice. According to Seamus Fernandez, vice president at the life sciences investment bank Leerink Swann (Boston), "It still has not permeated the pharma industry that payers are linking their assessments of the healthcare value of new therapies to market access. And I have yet to be in a company presentation where the actual value proposition of a product is proposed or discussed, excluding vaccines." Mike Raab, partner at venture capital firm New Enterprise Associates (Baltimore), says that "while it's changing, I think that during the development process, companies aren't thinking about payers as often as they should. I think a big reason why venture capitalists [VCs] haven't focused on this issue is that VCs are cashed out of companies historically before payers became an issue."

It is critical for those who want to compete now and in the future to understand how their drugs and research efforts stack up in a healthcare value or OBA analysis, and to understand how to leverage the opportunities for competitive advantage that OBA offers. And although many manufacturers are just starting to grasp the seriousness and implications of managed care payers' focus on healthcare value, payers are moving their agenda forward into uncharted terrain.

OBA encroaches on 'off-limits' diseases

Until recently, payers have largely exempted diseases deemed to be life threatening, such as HIV and cancer, from economic scrutiny. Yet unnoticed by most, some have already opened the door for scrutinizing the value of therapies for even the 'off-limits' diseases. For example, because HIV has evolved into more of a chronic disease with many treatment options, payers feel they are in a position to question how broadly new entrants, particularly those with very high price tags, should be used. As for cancer, over the past several years, we have had many conversations with managed care executives who have indicated great concern over the broad lack of healthcare value in new oncology treatments. They have also said they worry about appropriate utilization and cost trends.

Payers are very nervous about the potential for the oncology treatment bill to skyrocket. At nearly a 40% increase from 2005 to 2006, cancer was the fastest growing specialty pharmacy expense for ExpressScripts (St. Louis), one of the top three pharmacy benefit managers in the United States. According to a report from IMS Health on the cancer pipeline, (Norwalk, CT, USA), industry consultants nearly 400 compounds are in development (ref. 1) (**Fig. 3**). Adding to payers' concerns, researchers are expecting that the next stage for the treatment of many cancers will turn them into chronic diseases, requiring lifelong therapy. Finally, a good deal of cancer therapy relies on drug combinations. Payers fear that stacking very expensive biologics in such a fashion will lead to an affordability crisis.

Certainly managed care is building a case that many oncology treatments do rather little on average for patients, at a very high cost. One of the most cited examples is ImClone's (New York) Erbitux (cetuximab), an adjunctive treatment for end-stage colorectal cancer. Erbitux slows end-stage progression, extending average life expectancy for very sick patients for a few months. At a cost of over $10,000 per month of treatment for the drug alone (administrative and other costs raise the effective price), many payers point to Erbitux as 'Exhibit A' for demonstrating the lack of healthcare value in many oncology treatments. Unfortunately, the cost also prevents more widespread experimental use upstream in the disease progression where some hope to find benefit. And although Erbitux has become a blockbuster, drugs like it are acting as the tipping point for the development of new more restrictive policies for expensive oncology treatments.

This is not to say that all new targeted oncology drugs are dismissed as having questionable value. For example, Novartis' (Basel) Gleevec (imatinib), an oral treatment for Philadelphia-chromosome-positive chronic myeloid leukemia, is considered a dramatic improvement over the previous standard of care and thus still valuable at its price of over $26,000/year. In fact, unlike Erbitux, which has been rejected, initially and again upon appeal, by the UK's

Box 1 How OBA differs from evidence-based medicine

Many readers are no doubt familiar with the application of evidence-based medicine to inform treatment decisions. Although evidence-based medicine leverages strict clinical endpoint data from double-blind, placebo-controlled trials to develop treatment guidelines for physicians, OBA moves beyond these considerations, to encompass a broader range of potential drivers of treatment choice and thus provide guidelines that dictate payer coverage. In addition to clinical measures, OBA incorporates humanistic and economic considerations into the coverage decision-making process. Clinical outcomes are typically hard endpoints (e.g., an event like a stroke or death) or a clinical measurement (e.g., cholesterol level or tumor size). Humanistic measures are softer, including considerations such as improvements in patient symptoms, function and quality of life. Economic considerations include the level of savings accrued from avoiding costly adverse events (e.g., heart attacks or stroke) or costly surgeries and emergency room visits.

What's more, payers also want drug access decisions to be rooted in real-world outcomes, which often vary widely from strictly controlled clinical trials. And unlike previous market paradigms, OBA strips out any marketing-oriented advantages that do not result directly in improved outcomes but for which companies often justify price premiums, such as a new delivery system, a new method of action or combinations of otherwise available drugs. Although these 'advantages' play well in advertising, they do not always result in improvements in efficacy, safety or economics. And in such cases, payers are very likely to resist paying a higher price over the current standard of care (**Fig. 2**).

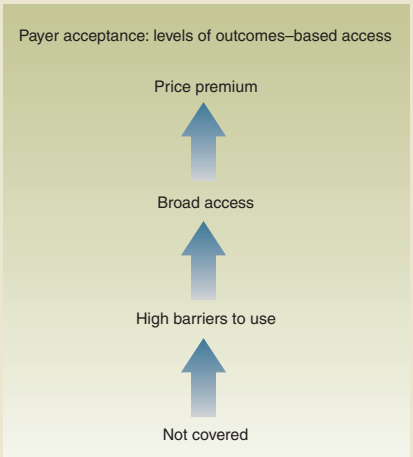

Figure 2 Continuum of a product's market access, based on payers' determination of its healthcare value.

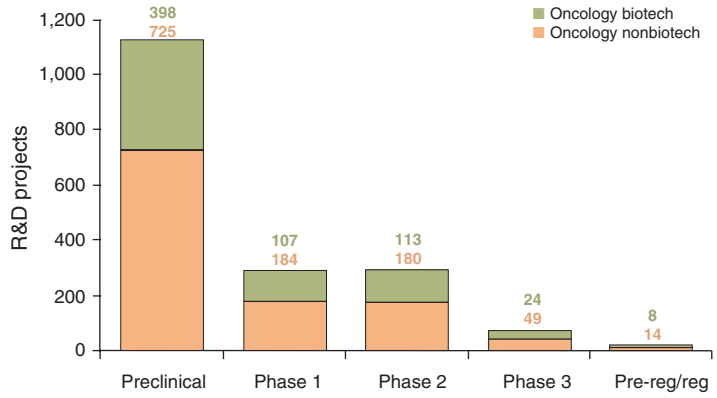

Figure 3 Biotech drugs in the oncology pipeline. Biotech is more than one-third of the late phase oncology pipeline. Source: IMS Health, Norwalk, CT, USA

cost-effectiveness watchdog. the National Institute for Clinical Excellence (NICE; London), Gleevec enjoys a first-line recommendation.

Analyses regarding the value of oncology drugs that extend life will continue to present an ethical dilemma. Although health economic and actuarial litmus tests do exist that place a value on life (e.g., the cost per quality adjusted life year, or cost/QALY), a measure of how much each additional year of life will cost, weighted by the patient's health level, as these issues move to the forefront, manufacturers and patient groups will dutifully challenge us to rethink how, as a society, we want to make such judgments.

Some of these changes are already underway. Managed care insurer Regence (Seattle) has always been a trailblazer of the OBA movement, often looked to as a leading edge of emerging policy. In 1998, Regence was the first in the United States to incorporate pharmacoeconomic evaluations as a requirement for small-molecule coverage. In 2007, Regence took another bold step, by beginning to shift administration of all oncology therapies to the pharmacy benefit, where they can be rigorously analyzed for value and controlled accordingly before any services are delivered. Regence expects this process to be completed and operational by 2009.

And make no mistake about it, Regence's actions are just a first step in a process that we believe will parallel the process that small-molecule therapies have experienced. What's more, Regence is not alone in taking these steps. Payers almost uniformly believe that many existing oncology therapies offer poor healthcare value, adding cost without anything approaching a corresponding improvement in patient health. And they are determined to do something about it.

The coming clash

At the same time that payers are stepping-up their application of OBA in biologics and expanding into previously off-limit disease areas, such as oncology, manufacturers and discovery companies are intensifying their investments in protein-based therapies in these areas. Yet the reality is that although these development decisions are being driven by prioritization of clinical need, they are also heavily motivated by the commonly held belief within the manufacturer and investor communities that new biologics, even those representing marginal advances, are likely to generate a relatively reliable and significant revenue stream, assured in part because of high unit prices. With the emergent payer attitude of control on the one hand and the diametrically opposed manufacturer mind-set for expansion on the other, a clash is inevitable. With so many new biologics on the horizon—many being developed for the same handful of conditions—and especially at a time when the bar is being raised by payers, we are likely to see far more losers than winners.

This imbalance is particularly true for oncology and inflammatory autoimmune diseases, all of which are heavily incorporated into the current business plans of many big pharma and biotech companies. For many biologics in oncology, the threshold for efficacy has been relatively low and the resulting revenue stream has been generous and easy to obtain. Given the new payer focus on oncology, in particular with respect to very expensive marginal products, the risk/return ratio for oncology investment may not be nearly as favorable as many perceive. As for the dozens of therapies in development for autoimmune diseases, there are now many well-understood, effective standard-of-care treatments with manageable though serious safety profiles, against which new treatments will be compared. Astellas Pharma's (Tokyo) Amevive (alefacept), which was developed as a psoriasis treatment by Biogen Idec (Cambridge, MA, USA) and eventually sold off after its disappointing market performance, is one such therapy in this area that failed to meet expectations due to an uncompetitive value proposition. Despite this, these diseases are still clearly areas of opportunity. One just needs to enter with caution and base assessments on what the market has become and where it is going, not what it was in the past, or otherwise assume that there have been no real changes.

Biosimilars will raise the healthcare value bar

The pending availability of biosimilars in the United States will further enhance the relative power of payers and their ability to compel greater healthcare value from biologics. The European Medicines Agency have put together a regulatory pathway to bring biosimilar therapies to European markets, and it is only a matter of time before biosimilar therapies are available in the United States.

Consider that standard-of-care therapies for many diseases, representing billions of dollars in revenue, such as cytopenia, multiple sclerosis and hepatitis C, among many others, are biologics whose patents have expired. The cost of these standard-of-care treatments will likely decline significantly once biosimilars become widely available. In practical terms, this means that new therapies entering markets with established bio-similar therapies will have an even higher value bar, needing to deliver greatly improved outcomes relative to increasingly cheaper standard-of-care therapies, to obtain a pricing premium. We see little evidence that manufacturers or investors are preparing appropriately for this eventuality.

We'd like to be clear—we are not suggesting that manufacturers and investors not pursue development of high-priced biological therapies. Rather, we believe that it is essential for manufacturers and investors to rethink their development and business models to ensure that they will be able to bring new therapies to market that will be successful in the ever-evolving payer climate. We believe strongly, in fact, that new biologics offer unprecedented opportunities to raise standards of care, provide new cures and improve the health of patients. But to maximize the opportunities, manufacturers and investors need to make changes. This next section highlights a few of our suggestions.

Developing products with high healthcare value

To adapt to this new environment in which payers will be scrutinizing health value propositions of new drugs, drug makers must, at the

very least, address three central challenges: (i) recognize the payer perspective and the incompatibility of current business models, (ii) take steps to restructure their models and processes accordingly and (iii) implement organizational changes to prioritize the development and delivery of healthcare value in all markets and across all functional areas of the enterprise.

Recognize the elevated role of payers and the centralized need for healthcare value. The current incarnation of the pharmaceutical industry built its success on centralizing the needs and expectations of patients and physicians. For years, the pharma industry has treated patients and physicians as their only real customers, developing products as well as marketing programs accordingly. In many quarters, pharma manufacturers, driven by pressure from a Wall Street spoiled by industry growth and incorporating ad agencies' branding focus, allowed true innovation and clinical need to take a back seat to a consumer product approach. There were few marketing problems that couldn't be solved by increased direct-to-

Box 2 How payers are implementing OBA

In a practical sense, OBA has been unfolding as a difficult-to-track patchwork of clinical guidelines, stopgap measures and caseworker decisions, forming a *de facto*, rather than strict standardized, policy. Without formal pronouncement of changes initiated by payers, many stakeholders—patients, physicians, manufacturers and investors—have been blindsided. Furthermore, with policies advancing in unchecked fashion, the healthcare community must decide which aspects are inevitable evolutions that appropriately address previous excesses and which are deserving of active resistance.

Payers have created a wide variety of policies and programs to help control drug use and mitigate costs, serving as the backdrop to enforce an OBA position. Many of these have been ported over to the management of biologics. Though these programs can clearly help target biologics to the most appropriate patient population, aid with compliance and avoid waste, they also can be taken to an extreme in which one can reasonably question whether patient access is being unduly restricted. Various programs tracked by The Bruckner Group are listed below, although this is not an exhaustive list.

Formulary and patient out-of-pocket. The formulary is a routinely revised list of those drugs available to a plan holder, organized by tier according to which products the insurer prefers for a particular therapeutic need. The higher the tier—most plans have 3 or 4—the more a patient will have to pay out of pocket to obtain the drug. The intent is that a nominal payment varying from $5–50 will provide patients with a financial incentive to choose the preferred drug. With many plans requiring a 20% out-of-pocket payment for biologicals, patients unable to pay the thousands required are *de facto* being denied access.

Authorizations and utilization reviews. For many drugs and virtually all biologics, physicians must obtain prior authorization from an insurance company before a drug can be provided to a patient. The complexity of a prior authorization can vary widely. Some simply restrict drugs to those for whom they are medically necessary, denying access for cosmetic reasons, for example. Others require a broad array of clinical tests, previous treatment failures and particular health status. Even with a complete and qualified prior authorization, physicians report inexplicable denials, which they must then take time to fight. Utilization reviews and frequent reauthorizations can lead to confusion, frustration, treatment gaps and treatment discontinuation.

Step therapy. Before some drugs are made available to patients, physicians must first try, and patients fail, specified alternative therapies. Assuming that a good number of patients will respond to a lower 'step', these policies can be an effective way of preventing knee-jerk use of expensive alternatives. At the same time, many patients and physicians feel that these programs just delay or prevent patients from being put on the best possible alternative as soon as possible, perhaps allowing progression and serious events that otherwise would have been avoided.

Guidelines as rules. Evidence-based clinical guidelines are intended to provide direction and assistance as physicians individualize a patient's care. Instead, guidelines are increasingly being misused as categorical rules that must be followed to the letter. For example, if clinical studies show that the majority of patients will respond to a particular dose within three months, payers will not make higher doses or longer durations available to physicians. These restrictions are enacted even in the face of additional evidence demonstrating that some patients would, in fact, respond with a more tailored therapeutic course. Similarly, drug labels are being strictly interpreted not only to restrict off-label use, but to minimize the population to whom a drug might be made available within the disease area for which it was approved.

Disease management. In its most elaborate form, disease management provides chronic disease patients with integrated care across all aspects of their lives, including clinical services, drug choice and compliance, nutrition, psychological support and education. Unfortunately, often for those on a biologic, what is called disease management is actually more like mandatory case management provided directly through the specialty pharmacy. In these programs, an insurance representative oversees and even 'approves' a physician's treatment plan, continually reviewing patient use to ensure proper compliance and avoid waste (that is, conforming to payer guidelines).

Physician profiling. Physicians contracted by payers are increasingly targeted as a conduit for payer pharmacy policy. Physician profiling for economic efficiency and prescribing patterns has become routine for specialties that commonly treat with expensive biologics. Dedicated payer personnel monitor physician use and address those whose use of expensive drugs is beyond some benchmark. With the increased application of pay-for-performance programs in which physician payment is linked to performance measures, including adherence to guidelines, it is only a matter of time before these programs make their way to biologicals management.

Box 3 Big pharma case study: Merck's enterprise-wide response to OBA

Although most large pharma and biotech manufacturers have recognized a problem and are now struggling to incorporate OBA and healthcare value into their business models, Merck (Whitehouse Station, NJ, USA) has taken path-breaking action. Recognizing that its existing structure and processes were insufficient to address the rise of payers and their now-central role in coverage, access and utilization decisions, in late 2005 Merck embarked on a two-year program to update its business model and centralize healthcare value as a mission-critical objective.

According to Merv Turner, Merck's senior vice president of worldwide licensing and external research (and coleader of the organizational redesign project), Merck formed much greater integration between research and commercialization franchise leaders to ensure that research targets and commercialization efforts were fully consistent and working together, rather than independently. "In the past, we would have been satisfied with proof of scientific concept; now we require proof of commercial concept [early in the process] also," Turner says.

One of Merck's greatest challenges was overcoming siloed functional capabilities that were largely autonomous, in an emergent environment that requires real cross-functional decision making. To address this challenge, the company developed and implemented an integrated R&D process that functionally brings together development, clinical, marketing and outcomes capabilities at all stages.

Merck also recognized the need to expand their focus to include payers as serious decision makers. "Merck now defines its customer value propositions in terms of our three primary constituents: physicians, payers and patients. We try to understand a drug's value proposition from each of their perspectives," says Mark Stejbach, Merck's vice president of managed care, who is one of the drivers of Merck's internal efforts. To ensure that healthcare value is at the center of each product development program, Stejbach adds "we seek to measure a new drug's profile against the standard of care, not just placebo."

Merck has clearly differentiated itself by recognizing the issues and taking action. We believe their choice to hit OBA head-on using early-stage cross-disciplinary development teams is likely to reap substantial commercial and financial gains in the coming years. Yet there are many different pathways to adapting to a healthcare value–driven environment. The pathway forward requires companies to approach these challenges in a manner consistent with their individual circumstances and culture. The only constant requirement is commitment.

consumer advertising or a larger sales force. From the top down, the industry has become entrenched with business models, corporate structures, business processes and even personnel development that have all but excluded payers as serious players and excluded economics as an essential determinant of value.

This was also the environment into which biologics were born. Human proteins offered an entirely new pathway for fighting disease, incorporating our advancing knowledge of genomics and proteomics. In the wave of excitement, no one dared to question their cost, which is orders of magnitude higher than most small molecules. It was enough to say that biologics were different and cutting edge, expensive to develop and manufacture.

As payers emerged as active players, questioning drug value and restricting use, drug companies simply were looking the other way and did not see the flashing red light on their dashboards. Biotech manufacturers, in particular, were caught off guard. Their interest in payers was limited to coverage—getting onto formularies, negotiating rebates, understanding what prior authorization forms were required and helping with rejected claims appeals.

As OBA unfolded, biotech manufacturers blamed any negative revenue or growth changes on what they were familiar with—poor sales force performance and marketing message deficiencies. Not until over a year after biologics copayments hit a prohibitively high 20% did biologics manufacturers realize the impact payers were having actively questioning use and using tools at their disposal to systematically affect patient access to biologics therapies. And as manufacturers began to address the copayment issue, payers had already moved on to more aggressive disease management and pay-for-performance programs. Because of their corporate structure, no one, even in the managed markets function, really had the responsibility to survey the payer landscape for such advanced programs. The front line, the sales force, was first to really witness OBA's impact, but because functions are so siloed—and in the case of some biotech companies sales is in the hands of a completely different company—this information did not arrive on the desk of someone who could take action.

OBA challenges manufacturers to return to the fundamentals of what made the pharmaceutical industry great—addressing unmet valuable clinical needs through innovation.

Restructure business models and processes to centralize healthcare value in product development. If we take a step back and think through the impact that OBA will have on R&D, it is clearly necessary to start with a reassessment of corporate business models. These models provide the context and framework for what therapies will be developed and how markets will be approached. Manufacturers must update their business models to place the development of therapeutics that offer meaningful healthcare value as a mission-critical enterprise goal. For some in big pharma, this appears to mean a shift away from 'me-too' or 'lifestyle' products, less reliance on blockbuster models and increased hopes for biologics success. Although a full exploration of these issues is beyond this article, we have learned that the process for corporate change rests on some fundamental questions:

1. Is your current long-term vision of the industry, risk and opportunity, compatible with the emergence of payers and outcomes-based access?
2. How can your current capabilities, assets and investment portfolio be realigned and redirected toward value creation for a triad of stakeholders—patients, physicians and payers?
3. What opportunities for corporate differentiation and competitive advantage emerge as a result of these analyses?

Regardless of the grand strategic direction upon which manufacturers embark, all must operationally address the issues posed by OBA on the following three fronts: first, realign or redesign departmental, functional and cross-functional structures, to allow 'OBA-compliant' processes to be carried out and second, raise the level of personnel expertise across all departments essential to OBA and foster cross-communication; and third, evolve business processes for discovery and

commercialization to focus on the development of products with demonstrable outcomes-based value, aligning payers as key decision-makers, alongside patients and physicians.

Overhaul organizational structures and functions. The current business processes in place at most pharma and biotech companies are incompatible with the development approach necessary to maximize the healthcare value of new therapeutics. New drug development—from research through commercialization—has traditionally been a serial process, passing from clinical through marketing and sales, with reimbursement considerations tacked onto the end. Functional areas work in relatively isolated silos, with very specific targets and priorities, not to mention their own vocabulary. Furthermore, outcomes and reimbursement groups have typically been understaffed and underfunded, long considered to be cost centers that have no direct impact on revenue generation. Sales and marketing have been treated as revenue centers, and seen as the engine of market growth, becoming bloated as a result. This bifurcated structure and the attitudes that foster its continuation are dinosaurs. They are simply not compatible with the current US healthcare market, and this business model requires an evolution or restructuring if the industry is to return to its high growth days. Downsizing sales forces and acquiring a few new compounds will not address the root problem.

It has become apparent to us that a long-term solution to the emergence of OBA requires a degree of corporate restructuring. Currently, some of the functions needed to successfully leverage value as a competitive tool are distributed across many departments and at inappropriate stages of the development process. Other needs are simply not assigned to any specific entity, and thus these slip through the cracks. In other words, in some cases information and expertise are not making their way to the right place at the right time, or alternatively are not being developed at all.

Among the many issues that need to be tackled, companies must raise to an executive-level office the responsibility for creating value propositions, ensuring drug access and centralizing payer needs. What's more, the functional silos that prevent the solicitation and integration of expert advice and fertile ideas across disciplines must be broken down. For example, outcomes research departments are likely to be underused for their specialized analytical services during trial design. Any insights they could otherwise provide, such as in setting relevant value-building endpoints or gathering important data, are lost. In a similar fashion, the strategic positioning capabilities of the marketing group and the payer insights of the managed markets group may not be appropriately leveraged or tapped at all during clinical trial design. The reverse is also true, with sales and marketing teams left in the dark with respect to available data and tools that can be used in their efforts. Outcomes, economic principles and the payer perspectives must be diffused throughout the enterprise, if manufacturers are going to successfully adapt to an OBA environment.

Because trials have historically been the domain of clinical development teams, and producing a good deal of OBA-related data is largely outside of their immediate goals, it is easy to see why cross-functional teams will be necessary to meet these goals. Clinical departments have little interest in expanding the complexity, scope, cost and timeline of their trials by adding in new requirements that may not appear central to FDA approval. At the same time they will not be the ones left without data required for value proposition development and will not face the consequences that such a deficit will have on managed markets, marketing and sales. Development teams and development decisions need to include real and ongoing participation from all key functions, including clinical, managed markets marketing, physician and patient marketing, R&D, and outcomes research and health economics. Although a variety of functional inputs is usually a part of due diligence and may be solicited at key time points, in most drug companies the current process is too spotty and has no teeth.

Once management has made a commitment to centralizing healthcare value as a mission-critical corporate objective, important other changes will need to be made across the enterprise. Personnel of all stripes will need retraining. Employees will need to understand the major shifts in power and structure that have taken place in the pharma and biotech industries over the past half-dozen years, which have elevated the role of healthcare value in drug coverage, access and utilization decisions. Appropriate training will include instruction on healthcare value, how it is measured, and how it can be leveraged for competitive advantage. Additional training will be required

Box 4 Small-biotech case study: CardioVascular BioTherapeutics centralizes healthcare value

Small, nimble biotech companies are ideally positioned to quickly adapt their development and commercialization processes to the current environment, centralizing healthcare value and capitalizing on the opportunities offered by an OBA paradigm. One of our clients, CardioVascular BioTherapeutics (CVBT; Henderson, NV, USA), is such a company. CVBT's mission includes the development of fibroblast growth factor-1 (CVBT-141H), a protein angiogenesis therapy for patients with advanced coronary artery disease and severe angina. Now in phase 2 of development, CVBT has consistently focused its attention on the drug's healthcare value, right alongside a demonstration of efficacy and safety.

"Proving that CVBT-141H grows new blood vessels, increases perfusion and alleviates angina is essential for CVBT," says Daniel Montano, the company's CEO. "But just as important is proving that CVBT-141H is cost-advantageous to use. CVBT's healthcare value strategy is a critical component of our overall commercialization plan," he adds.

From the earliest stages of development, Montano's strategy has been to understand and address payer needs, as well as to ensure the development of a therapy that payers, as key decision-makers and customers, would value. To this end, CVBT developed a preliminary healthcare value proposition for CVBT-141H during phase 1, mining clinical and economic benefits throughout the continuum of care that a late-stage cardiac patient would require.

"In our discussions with payers, they are astonished when we show them that we have a value proposition model at all for CVBT-141H, much less one which indicates use of our drug could reduce treatment costs of these expensive patients by 20% over a five-year period. The benefits that CVBT has already reaped in our payer relationships have surpassed our expectations," Montano says.

In addition to collecting clinical data, Montano indicated CVBT is rigorously collecting data needed to drive CVBT-141H's value proposition, including resource utilization, quality-of-life and long-term outcomes data. "The analytical process for maximizing healthcare value has informed our entire development process and taken us in unexpected directions," Montano comments. "It has helped direct us down pathways for clinical development and created a pricing scenario that promises great returns to our shareholders while still respecting the healthcare system's needs," he adds.

to insure smooth implementation of cross-functional business processes and decision-making apparatus. Rewards for risk-taking need to be adjusted to promote creative action that maximizes compelling healthcare value. Budgeting and compensation incentives may need to be reoriented and updated.

Retooling discovery and commercialization processes to maximize value

For most companies, many internal processes are inadequate when it comes to surveillance over payer action, understanding of payer motives, attitudes and policies, and mining and developing outcomes-based value throughout a product's lifecycle. Throughout our practice, we have identified nearly two dozen such targeted problems, from pipeline assessments through message development and post-marketing competition. We briefly address only three of the major issues below.

Designing trials that maximize and prove OBA value. To ensure that clinical development is harmonized with the aim of developing, maximizing and proving OBA value, we recommend that companies implement three main strategies. First, given the great expense and length of time it takes to develop a new drug, it behooves all involved to perform a simple 'OBA reality check' at the start. Such an analysis centralizes the level of clinical and economic outcomes that a new therapy would need to reach to gain broad market access and command a price premium in the anticipated future market into which that drug will launch. Manufacturers need to understand how high a bar has been set by current therapies with respect to clinical and economic outcomes. They should likewise obtain payers' perspectives with respect to the disease area and the need for new developments. In areas with rather efficacious and safe therapies, many treatment options, and especially inexpensive generics—potentially a major emerging barrier for biologics—manufacturers must consider that their therapeutic approach has to offer a genuine breakthrough to command a respectable price premium. On the other hand, such analyses should help guide manufacturers to those areas with the greatest opportunity for revenue development, even if a new drug represents an incremental but still significant improvement. These analyses provide a stripped-down view, integrating the needs of payers, physicians and patients, while providing a counterpoint to many of the recent driv-

Box 5 Dangers posed by OBA excesses

Clearly, OBA policies carry the danger of swinging the pendulum too far in the opposite direction. There is a real risk that, taken to inappropriate extremes, OBA policies will overly restrict access and choice to patients with reasonable medical need, perhaps resulting in diminished outcomes and higher costs (in some cases).

All stakeholders can agree that we must hold the system to high standards, directing dollars to the highest value opportunity and encouraging safe and effective use of the right treatments for the right patients. These are the principles espoused by an outcomes-based system. However, as insurance programs roll out OBA-based programming, there are some real negative consequences that come with policies that go too far or are engaged without appropriate planning.

Denying patients medically necessary care. Patient care must always come first and cannot be risked in the face of cost containment strategies. The system has already moved quite far from the heart of what insurance as a concept is meant to represent. A system is emerging in which 'coverage' does not equal 'access'. Even if a particular biologic, for example, is covered by an employer-funded policy, several programs will deny patient access to that drug, even in the face of it being considered medically necessary. Formularies, patient out-of-pocket expenses and prior authorizations have evolved well beyond their original intent. Managed-care executives, with whom we speak regularly, do not deny that demanding very high patient copayments, in the hundreds or even thousands, for example, presents a significant barrier to receiving treatment even for the eligible and those at disease risk. Step therapy programs, likewise, may necessitate that a patient be put on an inferior drug and fail before being allowed access to the state of the art. We have worked extensively with patient groups across many targeted disease areas, including psoriasis, rheumatoid arthritis and hemophilia; some affected individuals suffer disease progression and more deleterious outcomes as they move through these machinations and perhaps even give up.

Increasing downstream medical costs. In many cases, policies that delay or deny care in the name of pharmacy cost-savings will only create longer-term medical cost increases. Because pharmacy benefit managers do not share any risk on the medical side, it is in their best interest to keep drug costs down despite any downstream increase in medical expenditures. We have learned through our own payer studies that even in integrated insurance companies, with their own internal pharmacy benefit managers and specialty pharmacy, many of these decisions are made in a compartmentalized fashion. Though they strive to fulfill this mission, their systems and resources simply aren't adequate to perform all necessary integrated analyses of costs and outcomes. If the consequences of a policy are not fully understood in a rigorous fashion, perhaps they should be delayed or shelved.

Usurping the role of the physician. One critical fact must be restated. The central role of the physician in making clinical care decisions must be preserved and kept paramount. Unfortunately, we have already seen their role often usurped by clinical guidelines and usage policies. As early as 1999, physician groups at the American Association for the Study of Liver Diseases (Alexandria, VA, USA), for example, expressed fear that guidelines were being misused as categorical rules of treatment, invoked to deny physicians the opportunity to individualize patient care as they saw fit. Evidence-based medicine should not be abused in this fashion.

Stifling innovation. Taken to their extreme, OBA policies can stifle the diffusion of innovation, allowing access to revolutionary products only at a premium. If this occurs, investment in medical technologies and drugs will simply be too risky in many disease areas. Furthermore, this must not be allowed to trickle upstream, making areas of applied research less viable because reasonable treatments already exist. All major players in the system must strike a balance, understanding that innovation is often incremental, and setting value expectations, pricing and access accordingly.

ers of development, including me-too products and convenience improvements.

Second, engage a robust, purposefully directed process. It is essential for manufacturers to use the clinical trial process not just to define the safety and efficacy of a new therapeutic, but equally as important, to define and especially maximize the therapeutic's provable healthcare value. Targets that may not seem terribly interesting clinically may be the ones that create economic fireworks. The process of seeking to maximize a therapeutic's healthcare value is poorly understood and involves much more than throwing a few pharmacoeconomic analyses into the development mix. It requires an active process of measurement, seeking attainable high-value clinical targets that will enhance the value proposition, driving development toward them, and continually refining and improving the value proposition to maximize its strength.

Maximizing a therapeutic's healthcare value is a complex and iterative process that should start between the end of phase 1 and start of phase 2. The first step is assessing the upside and downside potential of your potential therapy by developing a preliminary value proposition. We have found TreeAge's (Williamstown, MA, USA) software (http://www.treeage.com) for decision analysis to be an excellent tool for building many of the necessary models. Once a preliminary value proposition is in hand, it is much easier to make decisions as to whether or not the prospective value proposition is competitive against the current and future standards of care, or what it may additionally require through clinical development. The value proposition should be revisited each time new data are available, all the way through phase 3 and even beyond.

To be clear, simply performing a few economic analyses, pharmacoeconomic assessments or outcomes analyses does not represent a value-based strategy. And in the absence of strategic guidance toward value maximization, manufacturers will not achieve the desired results. Yet we consistently encounter executives who believe they have the 'bases covered' when in fact they do not. Phamacoeconomic and outcomes research groups serve extremely important functions, but should never be held responsible for developing the essential business strategy that guides healthcare value development. They further do not track payer attitudes, needs or programming that OBA analyses and value propositions will address. These concepts go far beyond their expertise, training and responsibility. It's akin to asking a company's accounting department to raise capital.

More properly, value propositions are maximized through a creative process of actively mining opportunity, something that can only be achieved through a broad-based creative engagement. In effect, development teams need to find the right balance between what is clinically exciting and potentially attainable (clinical and R&D), what is the unmet market need and revenue opportunity (marketing) and what is clinically and economically valuable (health outcomes and health economics).

Our third and final recommendation for trial design is to look for value, well…everywhere. Value can be mined from a broad number of sources throughout the continuum of care delivery. Researchers must be diligent to obtain these data as development progresses. Otherwise, in the absence of data needed to demonstrate value, companies will have to rely on a patchwork of increasingly unacceptable abstract models. The Bruckner Group has developed comprehensive frameworks to creatively exhaust all possibilities for value development. Some of the broad categories in our frameworks include:

Hard clinical targets
Safety and side effects
Surrogate endpoints
Disease modification
Symptomatic improvement
Function and disability
Health-related quality of life
Patient use of healthcare resources
Care delivery, efficiency and setting
Operational advantages

Above all, manufacturers should be mindful of clinical trial basics. Payers are sophisticated, many with experience at pharma companies and the FDA. They are increasingly troubled by clinical data that emerge from trials lacking such basics as randomization, blinding, representative patient populations and proper controls. They immediately can recognize when clinical trials have been 'stacked', such as a comparator arm that is anything but the current standard of care at full prescribed strength. Though these designs are adequate for FDA needs, they belie the potential comparative value of the therapy. Without the appropriate head-to-head data, companies open themselves up to an array of revenue-reducing arguments from payers.

At launch and for some time thereafter, clinical trials must provide all of the data needed to address outcomes-based access challenges and payer needs. As a result, components of commercialization and value development that were previously either deemphasized or dealt with after FDA approval must be incorporated upstream into the trial process.

In addition, payers are more aggressively questioning the applicability of clinical trial data for determining real world clinical value, and thus patient access. Manufacturers must plan for post-marketing studies that examine their drugs' performance in a real-world setting. These data will be essential for overcoming future access restrictions. There are a variety of avenues that researchers can pursue in this regard, including real world clinical and economic trials and creating patient registries. Depending on the particular situation, following patients from FDA clinical trials for an extended period may produce significant data. Most importantly, the need for real-world data presents an opportunity for manufacturers and payers to collaborate on a solution.

Engaging payer decision-makers. Managed care payers are willing to work with companies that are *genuinely* trying to bring to market therapeutics that address payers' healthcare value needs. Yet it is rare for pharmaceutical, and especially biotech, companies to appropriately and earnestly engage payers during the development process of any new drug beyond advisory boards (which in reality do not represent much of a true dialog). Excluding payers from discovery and commercialization means virtually ignoring the customer that actually pays the bills—something unheard of in any other industry. Managed care payers feel, and not without reason, that historically pharma and biotech companies have largely paid lip service to payers' needs and have typically sought to circumvent rather than address them.

We believe strongly that the pathway to sustained long-term growth comes from building collaborative, mutually beneficial relationships between pharma and biotech companies and payers. What we are certain of is that manufacturers that appropriately reach out to payers, even during early stages of product developments, will find willing collaborators.

Outcomes-based pricing. The outcomes-based pricing concept places drug prices within a rational economic framework. Price is set at a level that is based on healthcare value—a therapy's absolute and relative outcomes advantages and their economic consequences. Such an evaluation takes into account the ability of a therapy to reduce morbidity, disability and mortality, as well as the degree to which the therapy's cost can be offset due to a reduction in healthcare utilization. Expanded evaluations might also include the value of increased work productivity. Pricing for the US market has never been based on such a rigorous and methodical economic assessment. When we first publicly described and advocated for the incorporation of outcomes-based pricing analyses into the decision-making process at a conference in 2004, our presentation was met with an overwhelming reception, both positive and negative. The more creative,

forward thinkers understood that such pricing skills would develop into standard analytic tools, whereas others could not fathom such a seemingly iconoclastic approach. Regardless, we had struck a serious chord, because pricing is one of the most critical issues facing the drug industry today.

It is difficult to get into a pricing discussion without more centrally addressing a root (and yet unstated) assumption that seems to be widely accepted, although little discussed, within pharma and biotech companies. That is, when it comes to pricing decisions, the prevailing belief (among both companies and Wall Street) is that manufacturers should charge what is perceived to be the highest possible price. Often, this means simply tagging a premium onto what others are charging for similar treatments, despite the fact that those products likewise were priced on shaky economic grounds. In many cases, price is determined based upon a desire to achieve certain revenue targets. With the exception of treatments for orphan diseases, which are necessarily priced within a revenue and return-centric framework, this paradigm is not compatible with the emergence of an OBA-based payer system.

Pricing practices have been driven by two concepts that are fast crumbling. First, that demand for therapeutics is inelastic, so that, within reason, the same number of individuals will use a drug regardless of cost. This belief probably made sense when no one was seriously looking at prices and overall spending. Now, we know for a fact that with the rise of OBA, price is scrutinized and basic concepts of affordability are questioned. Simple variations in patient out-of-pocket payment levels can cause wide swings in use. Furthermore, as payers see that a drug is priced in such a way that it delivers real value, their desire to overpolice its use relaxes. In fact, a favorable clinical and economic impact, as can be seen in many choices of diabetes care, can drive payers to want more use, better detection, early intervention, ongoing review and better compliance. The same can be said for Crohn's disease, for which significant cost offsets from avoiding hospitalization and surgery are an important part of treatment value.

As an admittedly simplified example, loosely rooted in reality, assume that a drug priced at $25,000/year has reached only 20% of those who are eligible for it, and annual revenues have plateaued at a billion dollars largely because of payer action preventing greater use. If administration of the drug results in a reduction in healthcare resource utilization by an offset of $5,000, the net cost of the drug to the insurance system is $20,000. But, if the drug's cost is lowered by 40% to $15,000, the net cost per patient goes down to $10,000—a cost much more in line with the drug's healthcare value. At this price, payers can spend the same total while delivering the drug to twice the number of patients. And for manufacturers, revenue will increase 25%.

Second, companies still believe that regardless of how they price a drug and how unhappy managed care payers are with that pricing, that manufacturers will be able to drive ample use by extensive physician and patient marketing. We believe this is a legacy approach, one that was valid and effective for many years, but which has now been superceded by events in the market—namely payers creating a mechanism and building an infrastructure to push back.

To summarize, more and more companies developing specialty pharmaceuticals are pricing their therapeutics at levels that lead employers and payers to challenge their affordability and value. As a result, payers are engaging a wide and expanding variety of approaches to limit use of those therapeutics. Although manufacturers are engaging this pricing strategy because they believe it leads to revenue maximization, in fact it is having the opposite effect, and in many cases companies are generating far lower revenues than possible. We believe that in many of today's markets, manufacturers can, in fact, increase revenues by engaging a different approach: pricing commensurate to healthcare value. By engaging OBA pricing analyses and incorporating them into their decision-making process, manufacturers will unleash the next stage of growth—by making payers allies who ensure that as many appropriate candidates as possible get treated.

We want to be clear: by no means are we saying that outcomes-based pricing means slashing prices and revenues. In fact, we feel that the opposite is true—it can increase revenues and even unit prices. As payers have said to us many times, they expect their pharmacy spending to increase as drugs that deliver value come to market, but will resist increases that are not measured to be beneficial or effective. Drugs that are developed within the right categories and/or in the right clinical context will drive a price premium based on concrete differentiation. But, drugs that do not offer vast improvements cannot be priced as ones that do; such pricing is essentially asking the system to subsidize a failure, something that it can no longer afford to do. One thing is for sure: if the drug industry does not take control of the pricing dilemma, we are likely to see a strong movement toward price controls.

Closing comments

Although payer realities have permanently altered the market for new biological therapies, some have commented that the pharma and biotech industries' best days are behind them. We could not disagree more strongly. There is still an outstanding need for new therapies that will push the boundaries of how we treat major diseases, in areas as diverse as cardiology, oncology, neurology, endocrinology and immunology. We very much believe that strong sustained growth is attainable, but how companies go about seeking such growth will have to change.

Pharma and biotech companies are struggling to develop a business model that allows them to resume the heady growth of the 1990s and much of this decade. A key element of success is centralizing development and delivery of healthcare value to payers, in addition to physicians and patients, as a mission-critical objective in a company's business model. Furthermore, manufacturers need to reinforce the development, maximization and delivery of healthcare value in all key functions, including R&D, clinical development, and marketing and sales. In any business, success comes when you address your customers' needs better than any of your competitors. Those pharma and biotech companies that understand this and respond to it accordingly and effectively, while avoiding the common mistakes still being made, will become the new industry leaders.

OBA represents an earnest attempt by the funders of the insurance system to understand, measure and acquire value for the system with every dollar spent. If this fails, because of a lack of cooperation, thoughtlessness, scarcity of resources or overzealous implementation (**Box 5**), the system will become increasingly underfunded and destabilized. This will only lead the healthcare system closer to a solution that includes a centralized cost-effectiveness decision making body, such as the UK's NICE, and broad price controls. For all the reasons described above and others, a solution must be found before such a drastic turn becomes inevitable.

We believe stakeholders must work together to ensure that the principle and practice of OBA bring the system to a higher place, ensuring patient access, encouraging innovation, offering a reasonable return on investment to manufacturers and retaining an independent free-market US healthcare system.

COMPETING INTERESTS STATEMENT
The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

1. IMS Health. IMS Health Reports Global Pharmaceutical Market Grew 7.0 Percent in 2006, to $643 Billion (IMS, Norwalk, CT, USA, March 20, 2007). <http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_80560241,00.html>