

BioCentury

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Back to School

Facing reality

BioCentury This Week

Cover Story

Facing Reality — While biotech has been buoyed on Wall Street and expectations mount for increasing numbers of breakthrough drugs, the 21st Back to School essay argues the drug industry has not yet addressed the realities of the marketplace.

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BioCentury 100™ Indicators

Week ended 8/30/13

PRICES

4045.20
dn 0.4%

VOLUME

643.4M shrs
up 17%

Heavy Hitters

With four full programs in breakthrough translational science, the SciBX Summit in Innovation in Drug Discovery & Development is open for online registration. Details follow A29.

NewsMakers Countdown

Barely a month remains to the 20th NewsMakers in the Biotech Industry. Registration is brisk. Don't miss out. Details and online link follow A29.

For the first time since the 2008 melt-down, nearly everything appears to be coming up roses for biopharma. Money is again flowing into the sector, **FDA**, **EMA** and Japan's **Pharmaceuticals and Medical Devices Agency** are reporting rising numbers of approvals, and new regulatory pathways promise to increase the speed of development and approval of drugs that could provide treatment breakthroughs for patients who are gravely ill.

But just as regulators and companies attempt to speed highly promising drugs to market based on abbreviated data packages, payers worldwide are making reimbursement contingent upon the kinds of data that can take years of postmarket experience to collect.

These pressures require drug companies to rethink the kinds of products that stand a chance of reimbursement, the types of evidence that payers will require, and the prices that will be paid for products that clear the first two hurdles.

While many biopharma companies are paying lip service to this reality,

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Heart Pumping

The American Heart Association is calling researchers, health professionals and investors to the first Heart Innovation Forum. Announcement follows A29.

BioCentury THIS WEEK

SUMMER'S OVER

Which Way Washington?

www.biocenturytv.com

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BioCentury's 21st Back to School essay argues that for many — if not most — lip service is all it is.

For drug developers, facing the reality actually will require at least four transformational changes of behavior.

It will require substantive engagement with patients and payers to share data that can answer essential questions about drug development and reimbursement — questions that no one stakeholder can answer on its own.

It will require changing pipelines and R&D programs to focus on meeting the needs of patients and payers as those two stakeholders define them.

It will require hands-on participation in health technology assessment, where drug developers should be contributing knowledge to improve the HTA process rather than fighting it.

Lastly, and least popularly, the drug industry is going to have to come to grips with the reality that the existing pricing paradigm is not sustainable. This is precisely the opposite of the direction companies are pursuing with their focus on Orphan drugs and ever-smaller cancer indications, which they expect will continue to be priced at eye-popping levels with eye-popping margins and a steady dose of price increases.

While this may make investors happy in the short run, Back to School argues it will be destructive to both the industry and its investors in the long run by making payer and public backlash even harsher than it already is.

The loss of pricing power is already evident in many countries and can only be expected to accelerate. If the drug industry acts as a naysayer and fails to participate in shaping the system that defines innovation, the system will relegate drug companies to vendor status and make decisions based mostly if not solely on cost.

While many in biopharma may say this prescription amounts to “sleeping with the enemy,” there really is no alternative.

Indeed, Back to School argues the

Exchange cornucopia

Health insurance plans sold in state exchanges created by the Affordable Care Act are required to provide 10 essential health benefits (EHBs), including prescription drugs. However, the number of drugs covered and the size of premiums, co-pays and cost-sharing will vary from state to state and from plan to plan.

The District of Columbia and 13 states have elected to run their own exchanges. The remaining states will have exchanges run by the federal government.

The minimum number of drugs that must be covered was based on a benchmark plan selected by each state. Formularies for most benchmark plans offer more than two drugs per class but vary in size.

For example, the benchmark plan for California — Kaiser Foundation Health Plan Small Group HMO — on average covers about 26% of drugs in a class. In some classes, only generics are covered.

In Virginia, Vermont and Washington, the benchmark plans cover more than 85% of drugs in a class with more branded options than the California plan.

Cost-sharing and co-pays for branded drugs will be high as plans try to keep premiums low, in part to be more economically attractive to healthy people who face a relatively low penalty for not obtaining insurance.

The penalty to forgo insurance is just \$95 per family in 2014, increasing to \$695 per family by 2016 — far less than the \$220-\$447 monthly premiums in states that have disclosed rates.

The co-pay structure also implies these plans expect to enroll sicker individuals.

The majority of plans disclosed so far have high co-pays of about \$50 and out-of-pocket expenses as high as 75% of the total drug cost for branded and specialty drugs. Generics would be priced much lower and have co-pays of \$5-\$10.

Details for plans in the federal exchange covering the remaining 37 states are expected this month (*see BioCentury, June 24*).

Enrollment starts on Oct. 1 for coverage beginning January 2014.

— Erin McCallister

reimbursement space is ripe for the kind of collaboration that has resulted in profound breakthroughs in regulatory innovation over the last several years.

The situation

Nobody is immune to the new realities of the marketplace. Not the big pharmas that do the lion's share of selling; not the tiny biotechs whose main customers are pharma BD&L groups; not payers struggling for ways to provide the required benefits to many more lives; and not patients whose needs are inadequately served by existing treatments.

Right now, the payers — public and private — are driving the car.

Agencies that explicitly or implicitly evaluate the cost-benefit of drugs have existed across Europe for decades. But

lately countries like Germany and France have raised the bar for demonstrating benefit and getting reimbursement. These austerity effects are itemized in the quarterly earnings statements of virtually all the global pharma players.

Meanwhile, implementation of the Patient Protection and Affordable Care Act (ACA) in the U.S. is expected to pump tens of millions of additional lives into government and private systems. In an effort to provide drugs and services required by the statute at affordable premiums, payers will design formularies to favor low-cost generics and limit use of newer drugs through higher cost-sharing, prior authorization and step-therapy requirements.

Some investors and companies recognize that stricter reimbursement is not a transient problem. These players are now putting their resources into assets with ever-higher levels of differentiation. And venture investors and pharmas are beginning to demand as much clarity as possible on the reimbursement profile of an asset at every stage of development — starting in discovery.

Nevertheless, too many companies are

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This Week in SciBX

Sleuthing for Toxicity — Immunocore, Adaptimmune and UPenn researchers have determined that off-target toxicity most likely caused the two fatalities in a cancer trial of affinity-enhanced T cell receptors. SciBX Table of Contents on A21.

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clinging to old definitions of innovation that are grounded in science but have little to do with patient or payer demands.

In addition, too many smaller biotechs focused on early development continue to think evidence of differentiation can be created later — and preferably by someone else, like a large partner.

It's not only small companies that aren't facing reality. One can find payers and patient groups that say the biggest pharma companies engage only cursorily to determine what innovations are most important, and what kinds of evidence could be used to show benefit.

Nevertheless, the healthcare marketplace is being reshaped by the kind of tension that creates conditions for a perfect storm, where all the stakeholders can be washed overboard.

A proliferation of new drugs — many first in class — is hitting the market in the midst of a worldwide economic crisis, and just as aging populations and healthcare reform are swelling the ranks of those seeking care under public and private insurance plans from the U.S. to China.

The number of drug approvals is soaring, driven by ever-more targeted therapies and the use of regulatory pathways designed to speed development and approval for novel medicines intended to treat serious conditions.

Approvals of new active substances have been on the rise in Europe since 2010. And in 2012, Japan approved the highest number of new active substances in a decade (see "Flooding the Market").

According to FDA, the 39 NMEs approved by CDER in calendar 2012 also was the highest in more than a decade — 63% higher than the nine-year average of 24 NMEs from 2003 through 2011.

"Many of these NMEs are notable for their potential positive impact and unique contributions to quality care and public health," FDA wrote in its Novel New Drugs Summary, released in January (see *Featured Links*, A28).

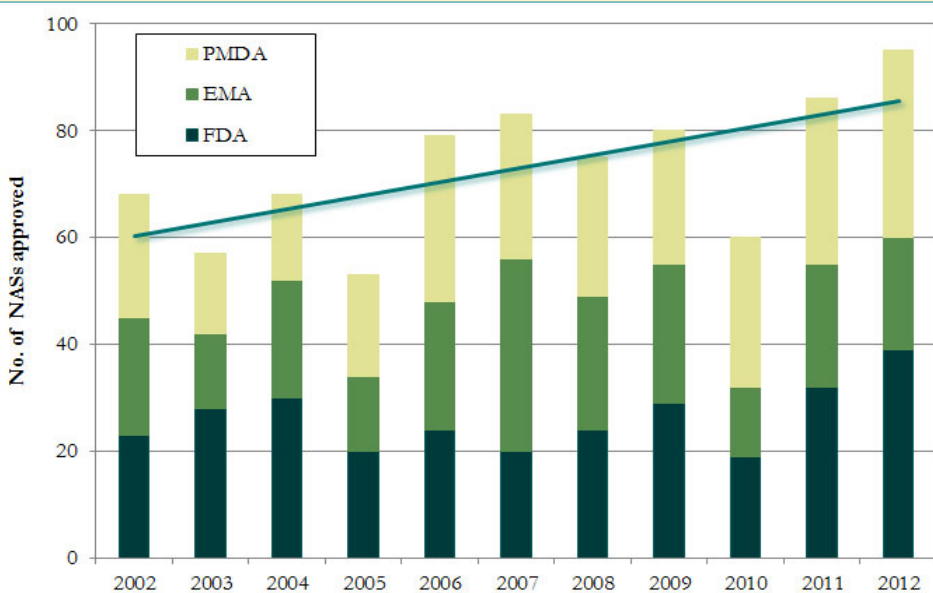
The agency considered 20 of the 39 NMEs approved in 2012 to be first in class, "meaning drugs which, for example, use a new and unique mechanism of action for treating a medical condition. First-in-Class is one indicator of the innovative nature of a drug and 51% First-in-Class approval rate suggests that the group of CY 2012 NMEs is a field of highly innovative new products."

In addition, 22 of the 39 NMEs CDER

Flooding the market

Based on data from the **Centre for Innovation in Regulatory Science (CIRS)**, the aggregate number of new active substance approvals in the U.S., EU and Japan reached 95 in 2012 — the highest in a decade. FDA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) each approved more than 30 NASs per year in 2011 and 2012. EMA's pace has been more deliberate: it has approved fewer than 30 NASs per year in the last 10 years, except in 2007 when the agency approved 36.

CIRS defines NAS as a "chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans" and that will be a prescription product to treat, prevent or diagnose human disease. Analysis excludes vaccines. *Source: CIRS*



approved last year received Fast Track designation, Priority Review and/or accelerated approval.

These numbers reflect the combined efforts of regulators, companies, legislators and patient groups that have labored for years to devise better ways of satisfying society's desire for new and better drugs. But it creates a conundrum for payers grappling with a tsunami of newly available — and almost universally expensive — products.

For instance, the total cost for one course of treatment with the 32 NME therapeutics that were approved by CDER in 2012 and have disclosed prices would be about \$2.4 million (see "Price of Innovation," A18).

The strain is being felt by government and private payers around the world but lately has been most visible in Europe, where austerity measures at the national level have placed an even higher premium on controlling healthcare costs than in the past.

In several cases, European HTAs and reimbursement authorities are recommending against or declining coverage of drugs that have received expedited approval based on what regulators consid-

ered to be strong evidence of the likelihood the drugs would meet unmet needs (see "G-BA Decisions," A4).

For example, the German HTA **Institute for Quality and Efficiency in Health Care (IQWiG)** issued a preliminary assessment that concluded **Pfizer Inc.**'s Xalkori crizotinib provided no additional benefit to non-small cell lung cancer patients compared with docetaxel or pemetrexed-containing chemotherapy.

By contrast, FDA and EMA considered the drug enough of an advance to grant accelerated approval in the U.S. and conditional approval in Europe based on an unprecedented 61% response rate in patients with locally advanced ALK-positive NSCLC.

Whether Xalkori can increase overall survival won't be known until confirmatory trials are completed. According to FDA's approval letter, the first trial should be complete by year end with a second trial to complete in December 2015.

After IQWiG's review, Pfizer submitted additional data that allowed the **German Federal Joint Committee (G-BA)** in May to conclude that Xalkori has "significant" additional benefit over chemo-

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therapies in its approved indication.

In its final assessment, G-BA said Xalkori leads to a clear improvement in quality of life and a clear reduction in non-serious disease symptoms vs. comparators.

It was a different story in the U.K., where neither additional analyses nor undisclosed discounts under a patient access scheme were enough to persuade the **National Institute for Health and Care Excellence (NICE)** to recommend the drug for use on the NHS.

Xalkori, a dual inhibitor of c-Met receptor tyrosine kinase and anaplastic lymphoma kinase (ALK) and their oncogenic variants, has received reimbursement in the U.S. The wholesale acquisition cost (WAC) for a month's supply is \$10,871.

U.S. payers typically cover cancer drugs included in medical compendia or treatment guidelines, and Xalkori is recommended as a first-line treatment for ALK-positive NSCLC patients in the **National Comprehensive Cancer Network's (NCCN) 2012 guidelines**.

UnitedHealthcare Group listed Xalkori as a Tier 2 drug on its 2013 formulary. While the specific copay is not listed on the formulary and Pfizer would not disclose the average copay for patients taking the drug, the pharma provides assistance which caps the monthly co-pay at \$100 for patients with private insurance.

As pricing pressures have continued to mount in Europe, pharmas have moved to shrink their European footprint with smaller commercial organizations and a narrower focus on key products or specialty areas (see *BioCentury*, Feb. 18).

In the short term, growth in emerging markets and more emphasis on U.S. launches could partially offset declines in European sales. But emerging markets, already driven by lower-margin generics and branded generics, also are facing overwhelming demands for care by underserved populations.

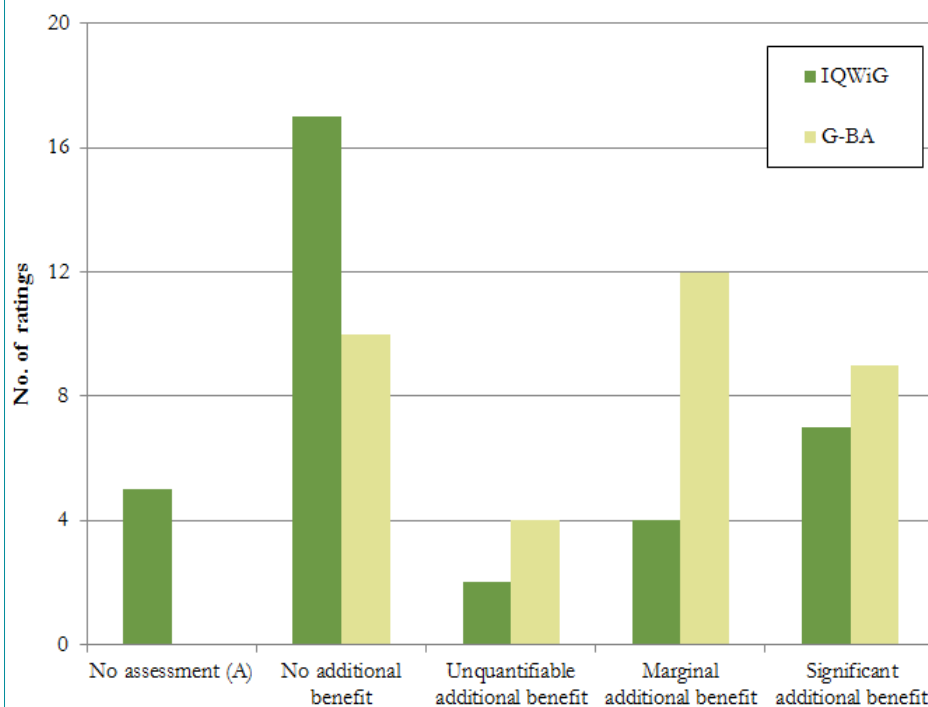
Meanwhile, healthcare reform will soon bring additional pricing pressures in the U.S. as up to 15 million new lives enter Medicaid and another 15 million who were under- or uninsured potentially enter state exchanges (see "Exchange Cornucopia," A2).

According to a May report by the Congressional Budget Office, Medicaid expansion will cost the federal government \$710 billion over 10 years. Under

G-BA decisions

Germany's **Federal Joint Committee (G-BA)** found no additional benefit for almost one-third of the 34 drugs it reviewed that are first-in-class and/or received an expedited review designation or Orphan Drug status from FDA or EMA. Germany's **Institute for Quality and Efficiency in Health Care (IQWiG)**, which makes the preliminary assessment, considered half of these drugs to have no additional benefit.

Expedited review designations include accelerated assessment in the EU, accelerated approval in the U.S., and Priority Review or Fast Track designation in the U.S. In cases where there was more than one rating per drug, the best rating was counted. A detailed list of the G-BA decisions is available [online](#). (A) Since early 2012, IQWiG has not conducted benefit assessments of Orphan drugs; Sources: *BCIQ: BioCentury Online Intelligence; G-BA*



ACA, the federal government pays 100% of the costs of Medicaid expansion in 2014-16, with federal contributions tapering off and eventually dropping to 90% in 2020 and thereafter. Medicaid is already dominated by generics and requires big discounts from manufacturers for branded drugs that are offered (see *Featured Links*, A28).

As an additional cost-containment measure, **CMS** issued a final rule in July that allows states to designate "preferred" drugs that have lower out-of-pocket maximums than non-preferred drugs.

The exchanges face a different cost-containment challenge as insurers struggle to balance the imperative to meet the minimum coverage requirements established by ACA with premiums low enough to attract customers in a transparent, competitive marketplace.

As one way of keeping premiums down, the majority of plans disclosed so far have high co-pays of about \$50 and out-of-

pocket expenses as high as 75% of the total drug cost for branded and specialty drugs. Generics would be priced much lower and have co-pays of \$5-\$10.

Another shoe yet may drop, as CMS has not shown its hand on whether companies will be permitted to offer co-pay assistance or other forms of financial relief to patients in exchanges.

Payers in the exchanges also are expected to use cost-containment practices like prior authorization and step therapy to steer patients toward generics and away from new and specialty drugs.

Payer groups like the **Academy of Managed Care Pharmacy (AMCP)** have argued these containment practices are necessary to promote efficient use of resources and to protect patients, especially in the case of new drugs where there aren't years of data to support their efficacy or safety.

Step therapy covers both goals by
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requiring cheaper drugs with known safety profiles to be used first.

"Step therapy is necessary for brand drugs because they often don't have the safety track record of generic drugs," Bernadette Eichelberger, director of pharmacy affairs at AMCP, told BioCentury.

One result is that some patients will almost certainly be deprived of new medicines.

According to Dan Mendelson, president and CEO of **Avalere Health LLC**, the firm's data show that pushing costs onto patients reduces adherence, even for life-saving drugs.

"We've done research at Avalere: for drugs that cost more than \$500 a year, if you put a 20% co-pay on those drugs, you'll get 25% non-adherence. That is for oral oncolytics," he told BioCentury.

Physicians, including some who make formulary decisions for hospitals, also are pushing back on drug prices.

In October 2012, three clinicians at **Memorial Sloan-Kettering Cancer Center** published an op-ed in *The New York Times* declaring that the hospital would exclude Zaltrap ziv-aflibercept from its formulary due to its high price.

Sanofi launched Zaltrap for metastatic colorectal cancer in August 2012 at a WAC of about \$9,600 per month for a 75 kg patient.

The price was intended to be comparable to that of metastatic colorectal cancer (mCRC) drug Avastin bevacizumab, which has a monthly WAC of about \$10,000 at the recommended dose. **Roche** and its **Genentech Inc.** unit market Avastin.

But doctors routinely use Avastin at half the recommended dose listed on the drug's label.

The Sloan-Kettering doctors said Zaltrap was no better than Avastin and that the \$2,000 co-pay for the drug was more than the monthly income of half of Medicare participants.

A month later, Sanofi bowed to the pressure and offered a 50% discount on the drug (see *BioCentury*, Nov. 19, 2012).

Physician protests are not limited to the U.S.

This April, an international group of self-described "experts" in chronic myelogenous leukemia (CML) published a commentary in the journal *Blood* decrying the high cost of cancer drugs. The group, which consisted of more than 100 oncologists from North America, Europe

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and Russia, Latin America, Australia and Asia, and the Middle East and Africa, used CML drug Gleevec imatinib from **Novartis AG** as an example.

Among the authors was Brian Drucker, a physician-scientist at **Oregon Health & Science University**, who obtained the compound from Novartis and developed it for CML.

According to the commentary, Gleevec was priced at \$30,000 annually when the drug was launched in the U.S. in 2001. By 2012, the price had tripled to \$92,000.

"Being one of the most successful cancer targeted therapies, imatinib may have set the pace for the rising cost of cancer drugs," the oncologists wrote.

"Of the many complex factors involved, price often seems to follow a simple formula: start with the price for the most recent similar drug on the market and price the new one within 10% to 20% of that price (usually higher). This is what happened with imatinib, priced in 2001 at \$2200 per month based on the price of interferon, which was then the standard treatment," they said.

The authors cited data from the Red Book online showing all five tyrosine kinase inhibitors approved to treat CML have prices between \$92,000 and \$138,000 in the U.S. According to prices provided by the authors who practice in other countries, the prices in Europe are about half that.

"A reasonable drug price should maintain healthy pharmaceutical company profits without being viewed as 'profiteering,'" the clinicians wrote.

The authors did not address where that line should be drawn. However, they

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added, "Advocating for lower drug prices is a necessity to save the lives of patients who cannot afford them."

The paper concluded: "We propose to begin the dialog by organizing regular meetings, involving all parties concerned, to address the reasons behind high cancer drug prices and offer solutions to reduce them. For CML, and for other cancers, we believe drug prices should reflect objective measures of benefit, but also should not exceed values that harm our patients and societies."

The path forward

It's been obvious for years that existing systems for funding and delivering healthcare all around the world are unsustainable. But austerity has made unsustainable costs today's problem, not tomorrow's.

Healthcare budgets are only going to become more strained as worldwide populations age, as more therapies become available for previously untreatable diseases and as highly effective therapies turn once-fatal diseases into chronic conditions requiring long-term treatment.

FDA's Janet Woodcock says the flood of breakthrough therapy designations is probably not an anomaly and is a result of the increased number of targeted therapies that present dramatic efficacy in early clinical trials (see "*Breakthrough Bolus*," A6).

Some of the solutions to better deploy limited funds to the most effective therapies are within industry's control; they are obvious and already the subject of robust efforts, such as trying to identify which patients will respond. Every large pharma and biotech, as well as many smaller companies, include biomarker strategies at the earliest stages of development.

But even though technologies such as cheap, fast sequencing should help identify markers predictive of efficacy and safety, researchers are still a long way from industrializing this process.

To date, FDA has approved only seven new drugs simultaneously with companion diagnostics.

Many drug companies have tried for years without success to find markers for drugs in use today, such as Genentech's Avastin, first approved in 2004, and multiple sclerosis drug Copaxone glatiramer acetate from **Teva Pharmaceutical Industries Ltd.**, which has been marketed in the U.S. since 1997 and Europe since 2000.

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But even if there were already a marker for every drug, society still could not bear the current rate of growth in drug expenditures. A paradigm shift is required.

While a detailed schematic for the solution can't yet be drawn — witness the tortured attempts represented by ACA in the U.S. and the AMNOG pricing law in Germany — Back to School sees at least four places where the drug industry must be prepared to transform itself.

For starters, it will be necessary to reorganize product development to improve patient outcomes as defined by the marketplace. This will require a much more significant level of engagement with all the stakeholders with the explicit aim of sharing data and resources to ask and answer specific questions about developing, using and valuing drugs.

In 2011, Back to School outlined the core questions that must be answered. Regulators, payers and patients must concur on what defines disease and what constitutes disease modification. With these benchmarks in hand, the pathway for drugs to achieve regulatory approval and reimbursement will be brightly lit (see *BioCentury*, Sept. 5, 2011).

While the drug industry and regulators are making strides on this front, Back to School now argues biopharma companies and payers must set aside historically adversarial relations and instead work together to find solutions that address each industry's economic pressures and ensure patients have access to new treatments that really work.

Continued one-off deals to lower prices for specific drugs will not be sufficient, and they require companies and payers to fight every battle for every drug anew. But such deals may provide models that could be adapted for more widespread use.

In addition, the ongoing experiments between payers and companies seeking to improve data collection as well as reshape the ways reimbursement are determined are a starting point that may lead to more scalable solutions.

The new models of collaboration will also engage patients throughout R&D, starting with defining the objective of a new drug — there is no point designing a drug to produce one result if what patients need most is something else.

As Back to School noted in 2011, the drug industry has embarked on hundreds of collaborative experiments with academics in the translational space. For 2013, Back to School argues this same kind of thinking must take place downstream.

The second major behavioral change: Drug companies must start creating the case for value differentiation in discovery and then steadily build a body of evidence throughout the product development process.

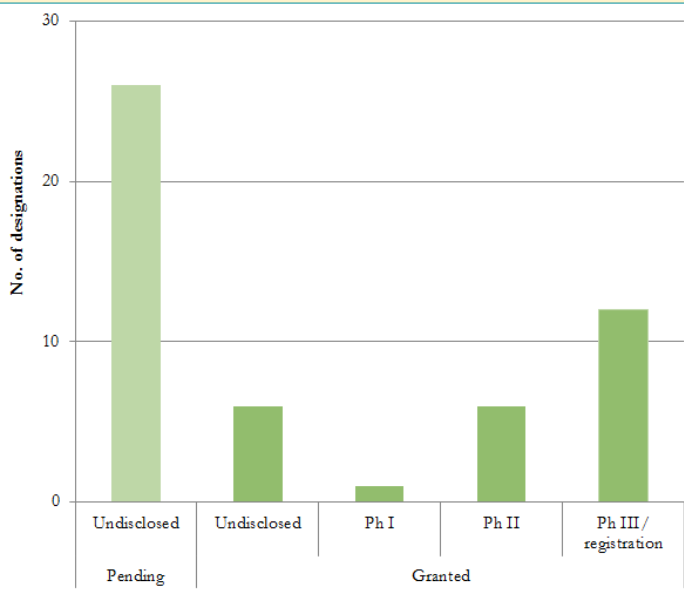
Some drug developers have figured this out and have reshaped both their pipelines and development practices accordingly. But the number of me-too and purportedly me-better products still in the pipeline — coupled with the fact that drugs are still getting to Phase III and beyond without comparisons to relevant SOC or data on quality of life and other metrics that patients value — shows efforts in this department are still wanting.

For example, BioCentury's BCIQ online database shows 54 compounds in active development that target VEGF or its receptors, not counting line extensions of approved VEGF and VEGF receptor inhibitors.

Even accounting for different variants of the receptor and its ligand and differences in delivery, formulation and dosing, it is

Breakthrough bolus

FDA has granted 25 breakthrough designations, including at least nine products already in Phase III or registration and thus potentially close to market. A further 26 requests are pending. FDA does not disclose the products, but the 19 breakthrough designations disclosed by companies as of Aug. 30 are available [online](#). Sources: BCIQ; BioCentury Online Intelligence; FDA; company press releases



highly unlikely that so many compounds could be differentiated sufficiently that physicians and patients would strongly prefer them to marketed alternatives — or that payers would be willing to reimburse them without restrictions.

In the lip service department, there also appears to be a discrepancy between how important companies say differentiation is, and what they intend to do about it.

A survey conducted by **Ernst & Young** of 62 European and U.S. companies with revenues below \$500 million showed nearly 100% of respondents said prioritizing product candidates that exceed SOC and demonstrating value of products to payers was “important” or “very important.” Few companies said these issues were “unimportant,” and none rated them “very unimportant.”

However, while 50% of respondents said they had already eliminated or were “very likely” to eliminate product candidates that might not exceed SOC, 21% said they were “unlikely” to do so.

More than 45% said they were “unlikely” to add payer/reimbursement expertise to their management teams, clinical development teams or boards of directors. Very few said they already had.

Given how long companies have known the day of reckoning on comparative efficacy is coming, these numbers are appalling.

As to the third behavioral change, Back to School argues bio-industry must abandon efforts to block third-party assessments of value, and instead ramp up nascent efforts to be at the table where technology assessment takes place in the U.S., Europe and the rest of the world.

Comparative effectiveness and cost effectiveness assessments will not be stopped. Industry can either contribute its expertise to improve the quality of the results, or stand by while others

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who may know less about both the drugs and the best ways to study them do the work based on their own priorities. Right now that priority is finding ways to avoid paying for new drugs.

The fourth behavioral change will be bitter medicine. Drug companies will have to charge lower prices for many drugs and engage with payers and patients in developing a new consensus on value for money.

This means margins also will fall unless companies can find efficiencies elsewhere, for example via “pro-competitive collaboration” as described in the 2011 Back to School — or cutting the fat everyone knows still exists in both R&D and sales and marketing at large companies.

It is not obvious how drug companies can persuade investors to forgo the short-term gains that can be achieved on the back of exorbitant prices for drugs that provide marginal benefits, or that must be used in combinations or cocktails that layer on cost, particularly in cancer.

What is obvious is that blindly continuing on the current pricing path will only drive the system to the breaking point, after which the window will close on industry’s ability to contribute solutions.

Connecting with stakeholders

It will be necessary to reorganize product development to improve patient outcomes as defined by the marketplace. This will require a much more significant level of engagement with all the stakeholders with the explicit aim of sharing data and resources to ask and answer specific questions about developing, using and valuing drugs.

The very pressures that are squeezing drug developers, payers and patients make the reimbursement space ripe for the kind of collaboration that has produced breakthroughs elsewhere in the drug development continuum.

For example, the common interests of FDA, industry and patient advocates led to the swift reauthorization of PDUFA V legislation that includes an expedited pathway for breakthrough therapies, opportunities for patients to provide direct input into regulatory decision-making via disease-focused meetings, and a benefit-risk framework that should improve consistency of regulatory decisions and predictability for drug developers (see *BioCentury*, July 2, 2012).

Similarly, patients, payers and industry

The reimbursement space is ripe for the kind of collaboration that has produced breakthroughs elsewhere in the drug development continuum.

have common goals when it comes to creating what Back to School in 2007 called “New Value.”

As it was defined, New Value was created by three means. First was solving unmet medical needs, including providing alternatives for patients who do not respond to available therapies. Second was creating much better — not marginally better — alternatives to existing therapies. Third, and most important, was enabling patient access to these kinds of innovations (see *BioCentury*, Sept. 3, 2007).

In today’s terms, this means patients need better treatments that improve quantity and quality of life at an affordable cost. Governments and commercial insurers need to improve outcomes for beneficiaries while maintaining or reducing costs. And drug companies need information that can be used to prioritize pipelines and design development programs that have higher likelihoods of resulting in approval, reimbursement and uptake of new drugs.

“There is a mutual and shared interest between pharma and managed care in making sure patients get the meds they need and the implicit contract of insurance is maintained and improved over time,” said Avalere’s Mendelson.

Given that each side’s objectives look irreconcilable, the question is how to get started.

“The Pfizer shareholder always wants a higher price, and the shareholders of UnitedHealthcare a lower. Can there be win-win situations?” said Mendelson. “There are some cases where having the right drug at the right time will improve the bottom line of the insurance company. There are other cases where patients expect coverage even if it costs the insurance company.”

Right now, the solutions aren’t obvious because none of the stakeholders has a 360° view of how a drug affects the healthcare system, the value generated by that drug and how that value feeds back into the system.

Providers have real-world data including laboratory results, vital statistics and prescriptions that were written. But they

do not necessarily know whether prescriptions are filled.

Payers and pharmacy benefit managers see only claims data including diagnoses and prescriptions that are filled.

And only patients hold real-world information on whether and how frequently they actually take a drug, the extent to which it alleviates disease symptoms or causes side effects and how it affects their lives.

Meanwhile, industry is the biggest repository of detailed clinical data and information on the conditions under which a drug works best.

Companies and payers have been arriving at deals focused on specific drugs that are enabling access for patients when long-term outcomes are uncertain. But most of these are adversarial in nature — as when NICE uses HTAs to extract discounts from companies.

And in most cases there is little evidence that information is being collected that could be fed back into the system to improve care beyond that involving the specific drug included in the deal.

The good news is payers and patients finally are hungry for increased collaboration, and experiments are under way that could lead to scalable models of collaboration.

Edmund Pezalla, national director of pharmacy, policy and strategy at **Aetna Inc.**, noted pharma companies have expertise that can help payers learn how to better utilize drugs. “They have a good idea of how long does it take to see the effectiveness of this medication, and many other things,” he told *BioCentury*.

Indeed, a few large pharmas are beginning to partner with payers to develop data on outcomes that can be mutually beneficial (see “Partnering with Payers,” A19).

For example, in 2011, **AstraZeneca plc** and **HealthCore Inc.**, the outcomes research unit of **WellPoint Inc.**, partnered to conduct real-world outcomes studies in the U.S.

Another example comes from the U.K., where NICE and **GlaxoSmithKline plc** have been working together since 2009 to improve outcomes in chronic obstructive pulmonary disease (COPD).

The U.K.’s **British Lung Foundation** identified areas of the country with high rates of COPD prevalence and/or poor treatment outcomes based on the number of patients hospitalized for the disease.

GSK then worked with local primary care trusts and doctors to improve aware-

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ness of treatment options and proper use of COPD treatments, including drugs from GSK and other companies.

According to a report issued by NHS this year, in the Sunderland area, the program resulted in a 12% reduction in unscheduled hospital admissions and a 6% increase in patients receiving combination treatment in line with NICE COPD treatment guidelines.

In case studies detailing the program, GSK notes the project has provided increased awareness and uptake of the pharma's COPD treatments.

NICE has similar partnerships with AZ for COPD and with Teva for asthma.

"We need to have these partnerships where they are part of the solution because manufacturers play such an important role," said Mark Cziraky, Healthcore's VP of industry-sponsored research. These collaborations can help payers "find quality products for the population that will benefit."

But for the most part, such joint efforts are still novel. Drug companies primarily interact with payers to get feedback on or negotiate reimbursement for a particular product — usually very late in development.

If companies were to engage with payers earlier, a trove of information would be available for designing trials that produce data to support reimbursement.

The same is equally true of outreach to patients, if not more so.

"We have an opportunity as a patient-driven organization to drive discussion towards innovation and get access to life-saving treatments," said Scott Riccio, VP for advocacy and external affairs at the **Leukemia and Lymphoma Society**. "Patient groups are in a unique position because we can bring aggregate data that is unencumbered from motives of provider or manufacturers. We can help foster a better discussion."

But Riccio and Marc Boutin, EVP and COO of the **National Health Council** (NHC), say the patient piece is almost entirely missing.

According to Boutin, most drug companies rely on physician input — which is not the same as patient input — in Phase III and later.

"It's about engaging the patient really at the front end," he said. "Usually, information about the patient is gathered through representatives, third parties — usually healthcare providers, whose per-

spectives are different than patients'. Usually this is collected in Phase III or postmarket, which means the target you shot at was not defined by patients at the front end. At that point, it's too late."

Furthermore, said Boutin, patient information inside drug companies is not only spotty, but siloed across different parts of the development organization. "It's not coordinated, not strategic," he said.

Even worse, said Riccio, when discussion about value does occur, "it is almost singularly about value to the payer from how they perceive cost."

If companies instead engaged with patients to define what product characteristics they value and what outcomes are most meaningful, it could change the target product profile and result in higher-valued products — while helping con-


vince payers that these are drugs that must be reimbursed.


Boutin said Sanofi's **Genzyme Corp.** unit is the rare example of a company that engages patients from beginning to end.

"Genzyme brought the patient into the front end and engaged all the way to postmarket. They say there is no person who takes the company's medicines who is not touched by the company. Their engagement is intensive and one-on-one," he said.

This one-on-one approach is not scalable to much bigger diseases, but Boutin argued companies working outside of rare diseases can use social media, online surveys and similar media to get valuable input that could direct scarce resources into the highest-value programs.

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Congress cranks back up on Sept. 9. What does the rest of the year have in store for the Affordable Care Act, life science innovation and the biotech bull market?

Lawmakers will have three weeks to avoid a government budget shutdown.

Beyond the partisan brinkmanship and political spectacle, decisions made in the next three months will have real consequences for patients, NIH, FDA and investors in life science innovation.

The newest edition of *BioCentury This Week* television gathers its team of correspondents to anticipate the headlines.

Washington Editor **Steve Usdin**, Senior Writer **Erin McCallister** and Publisher **Eric Pierce** share their expectations for the big stories BioCentury will be covering as the nation's political leaders struggle to make decisions throughout the fall.

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idea: Industry should spearhead multi-stakeholder meetings focused on specific diseases at which patients, payers, companies, researchers and regulators could get common issues on the table to arrive at a shared understanding of need and value.

The Patient-Focused Drug Development meetings FDA committed to under PDUFA V could provide a model. While it's early days — the agency has only held three so far — the idea is to provide a forum that will embed patient perspectives into the regulatory decision-making framework (see *BioCentury*, May 6).

"We would love to see that same sort of robust engagement around the value discussion," Riccio said.

Boutin said upping patient engagement will require both a cultural shift within industry and the payer community, as well as new tools and standards to ensure meaningful and interpretable results. He said the National Health Council is working on new tools that it hopes will facilitate greater patient engagement.

"We have the will and we're going to try to catalyze it. But no one stakeholder has the clout to make it happen," he acknowledged. "The challenge for innovators, regulators, health technology folks

and payers is that we don't have a standard for what it means to engage patients and to train people."

Differentiation or bust

Drug companies must start creating the case for value differentiation in discovery and then steadily build a body of evidence throughout the product development process.

Meeting the marketplace demands for New Value requires different kinds of data, and more of it, than industry has routinely produced premarket. While certain kinds of real-world outcomes data can be accumulated only after approval, there is a lot companies can do — and Back to School argues must do — to support differentiation starting in early product development.

Doing head-to-head studies and incorporating measures that patients and payers recognize as indicators of value cannot be left for Phase III. Savvy drug developers will find ways to structure preclinical and clinical development to provide data that show their drugs will solve problems for their customers.

FDA's breakthrough drugs pathway provides benchmarks for this kind of thinking. It will reward drug developers who can design programs to show early signals of profound efficacy that can be validated quickly in the clinic.

But even in these cases, drug sponsors

can no longer assume they will be automatically reimbursed for high-need indications such as rare diseases or cancer, or that they will be immune to demands for outcomes data.

This means companies in discovery or preclinical development should already be developing a target product profile that supports the reimbursement case.

"You have to have an idea at the outset of how you are going to be better. Not *post hoc*," said Richard Pops, chairman and CEO of **Alkermes plc**.

Even small companies can collect a lot of data without clinical trials to help support product differentiation. Examples include data on burden of illness, the competitive landscape and the effectiveness of existing drugs that can be used as comparators.

Alkermes' depression candidate is a case in point. ALKS 5461 is a combination of the opioid receptor modulator ALKS 33 and buprenorphine.

Before development began, said Pops, research on the natural history of depression, patient responses to treatments and options for non-responders allowed the company to identify a target population of patients who do not respond to antidepressants and are moved on to more expensive antipsychotics.

The compound now is in Phase II testing to treat depression in patients who

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ABCs of ACOs

Accountable care organizations are an emerging model in healthcare designed to improve patient outcomes while reducing costs by reimbursing providers based on those metrics.

The Affordable Care Act created two ACO programs managed by **CMS** — the Medicare Shared Savings Program and the Pioneer ACO model.

The first was designed to facilitate coordination and cooperation among providers to improve quality of care for Medicare fee-for-service beneficiaries while reducing unnecessary costs.

The Pioneer model is for healthcare organizations and providers already experienced at coordinating care for patients across care settings.

Both programs will reward ACOs that reduce the growth in costs while meeting quality of care performance standards.

Shared Savings Program providers receive up to 60% of the savings if quality targets are met, while they continue to receive fee-for-service payments.

The savings ratio in the Pioneer program is undisclosed but the proportion of savings that goes to the ACO is higher than in the Shared Savings program. For the first two years, Pioneer ACOs are paid fee-for-service plus a shared savings component. They will shift to population-based payment and full risk arrangements in the third year.

ACOs in both programs are evaluated on 33 quality measures, including seven associated with the patient/caregiver experience. Six relate to care coordination, including hospital admissions. Eight cover preventative health, including breast cancer screening; and 12 are associated with at-risk groups such as LDL control in diabetics.

CMS will monitor ACOs to ensure they do not avoid at-risk patients.

Pioneer was launched in 2012 with 32 ACOs. In July, CMS reported the combined costs in these ACOs grew by only 0.3% in 2012 compared to 0.8% for other Medicare beneficiaries.

Thirteen ACOs produced gross savings of \$87.6 million and earned over \$76 million from the shared incentives. Two of the program's ACOs had total losses of \$4 million because their costs exceeded their expenditure benchmarks.

There are 106 ACOs participating in Shared Savings, and CMS expects to report data on the program this year.

The ACO model is also being adopted by private payers. For example, **United-Healthcare Group** in July said it expects its reimbursements via accountable care contracts to increase to \$50 billion from \$20 billion by 2017.

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have failed at least one prior antidepressant.

Once in the clinic, every trial should be looking at health outcomes endpoints on top of the primary and secondary endpoints required by regulators.

Pharmacoeconomic and quality of life metrics are at the top of the list.

Pharmacoeconomic measures include things like reductions in hospitalization, complications and concomitant medications, which can be combined to illustrate the overall effects of a new drug on the total cost of care.

Most QOL measures will include patient-reported outcomes (PROs) that measure how patients feel, the effects of treatment on daily life, attitude and the like.

No diseases are exempt from these evidence requirements, not even Orphan diseases.

"If you have an Orphan disease and it tends to be fatal in early adulthood and you have shown a positive impact on survival, then you've done something," said Aetna's Pezalla. "But if the clinical endpoint in the pivotal trials is a function status endpoint or the endpoint is only reached in patients with certain characteristics or who haven't progressed to a certain level of disease, we have to have more information on what will this medicine do and who will really benefit."

It is not prohibitively more expensive to incorporate health outcomes measures into early development, especially considering the cost of waiting until after Phase III or approval only to find nobody will pay for the drug.

"They should be looking at the burden of illness and should be thinking about adding health outcomes as endpoints to trials — things like quality of life and economics. Every trial should look at that; it's not that big a burden," said Richard Gliklich, president of Quintiles Outcomes.

CRO Quintiles Transnational Corp. created Quintiles Outcomes to conduct late stage trials and real-world studies including observational studies and studies using electronic health records and databases.

While having a more robust evidence package at launch will lessen the postapproval burden, measuring real-world outcomes still will be required. Even here, however, drug developers can be thinking about how their clinical studies can better mimic real-world conditions prior to launch.

Meeting the marketplace demands for New Value requires different kinds of data, and more of it, than industry has routinely produced premarket.

For example, in 2012, GSK started the one-year Salford Lung study of Breo fluticasone furoate/vilanterol in 4,000 patients with COPD and 5,000 patients with asthma.

The trial, which began a year before Breo was approved for COPD, is using electronic medical records to track the adherence and outcomes of patients given Breo vs. existing maintenance therapies.

To meet all these evidence tests, small companies may have no choice but to bring in commercial and reimbursement expertise much earlier than has been typical.

Anand Mehra, general partner at **Sofinnova Ventures**, said he is bringing in more commercially savvy CEOs and/or commercial officers at least by Phase II, and sometimes even earlier.

Even then, Back to School acknowledges it will be challenging to pinpoint the endpoints that will have meaning for payers and patients.

Gliklich suggested the comparative effectiveness research by the **Patient-Centered Outcomes Research Institute (PCORI)** and **Agency for Healthcare Research and Quality (AHRQ)** will provide some clues.

While Gliklich acknowledged these government bodies are controversial in the industry, he noted their model for stakeholder engagement is transportable.

In fact, the marketplace already provides alternative routes for building an evidence roadmap, and Back to School proposes drug companies pursue them.

In the U.S., more so than in Europe, the fragmentation of healthcare budgets can make pharmacoeconomic endpoints tricky. Because the medical and pharmacy side of healthcare are often paid for out of separate buckets, it may be difficult to get credit for a pharmacy drug that lowers medical costs either through reduced hospitalizations or reductions in disease recurrence.

But integrated health systems and emerging accountable care organizations (ACOs), along with Medicare Advantage providers, hospitals and large physician

groups, now are providing opportunities for drug companies to develop evidence through partnerships.

"If a company is capable of reducing readmission or improving the quality scores of a Medicare Advantage plan, that product could drive significant revenues to the organization," said Avalere's Mendelson. "We see more proactive companies really calibrating their clinical endpoints to prove they are able to improve the bottom line of the organizations they are targeting."

ACOs are compensated on their ability to improve outcomes while reducing overall healthcare costs (see "ABCs of ACOs," A9).

"The whole point of the ACO is that the payer, the pharmacy benefits manager, and the provider are all coming up with a care path that considers both pieces of the value equation. So there are drugs that may be more expensive at the front end, but may be more effective at the back end if they save on things like hospitalizations or complications," said Bruce Rogen, medical director of employee health services at the **Cleveland Clinic**, which operates an ACO.

The clinic's ACO includes primary care physicians, medical assistants, pharmacists, case managers and nurses, with a focus on chronic conditions.

Rogen said ACOs would welcome the opportunity to work with drug companies that can demonstrate a potential to improve patient outcomes and/or reduce costs.

Assessing value

Bio-industry must abandon efforts to block third-party assessments of value, and instead ramp up nascent efforts to be at the table where technology assessment takes place in the U.S., Europe and the rest of the world.

Purchasers will try to assess the value of products on offer with or without the drug industry's participation.

The state of Medicare coverage of molecular diagnostics is a good example of what happens when industry throws up roadblocks. Companies selling laboratory-developed tests (LDTs) have battled for at least a decade to prevent FDA from imposing premarket clinical utility requirements. Now local Medicare contractors are doing it instead.

Empowered by a new CMS coding system that for the first time gives payers information about the molecular diagnostic tests they are being asked to cover, many Medicare contractors are making

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coverage contingent on evidence of clinical utility, defined broadly as information leading to improved outcomes or physician decision-making (see *BioCentury*, July 15).

The problem is many of these contractors — who make the majority of payment decisions — lack the expertise and resources to operate a rigorous, consistent and transparent assessment process.

As a result, there are no clear or consistent standards for demonstrating “utility” to support coverage.

Kevin Conroy, president and CEO of diagnostic company **Exact Sciences Corp.**, summed up the industry’s conundrum for BioCentury in July.

“The question is, what is the level of evidence required, and what forms of economic analysis are required, and at end of the day, do those analyses result in incentives that cause innovators to make the significant investments needed to develop those tests?” he said.

As a result of payer decisions that appear inconsistent at best and arbitrary at worst, several VCs have abandoned diagnostics investing (see *BioCentury*, May 13).

Again, as is the recurring theme of Back to School in 2013, a much better model would be for industry to work with HTA agencies and payers to develop new ways of assessing value. This is happening to varying degrees in Europe.

It is too early to know whether or how

these efforts will affect assessments or how assessments of value will translate into reimbursement. But the point is that industry must have a seat at the HTA table.

For example, the **European Federation of Pharmaceutical Industries and Associations (EFPIA)** is working with the **European Network for Health Technology Assessment (EUnetHTA)** to move toward a mutual recognition-type process for the common elements of HTA, such as relative efficacy assessments of new drugs compared with SOC.

EUnetHTA is a group of government-appointed organizations, regional agencies and not-for-profits that produce or contribute to health technology assessments in 29 European countries, including 26 EU member states.

On July 3, EFPIA and EUnetHTA announced the trade association would facilitate the involvement of pharmaceutical companies in a pilot to conduct relative efficacy assessments (REAs) on 10 drugs; complete three full HTAs on drugs, devices or other interventions; provide early scientific advice on pharmaceuticals; and develop a template for submissions.

Drug manufacturers will be asked to propose compounds for the pilots, provide information about the compounds selected and contribute information about their experiences with existing HTA systems.

The work is intended to support a permanent, voluntary network of HTA agencies that will be managed by the **European Commission** and is to be set up by October.

However, Francois Bouvy, EFPIA’s director and team leader for market access, told BioCentury he does not expect a common REA to be developed or implemented in the short term.

In a separate process, EFPIA is providing input into a pilot led by EMA and EUnetHTA to develop a process for joint rather than parallel scientific advice involving regulators and HTA authorities. According to Edith Frenoy, director of HTA at EFPIA, 15-20 joint scientific advice sessions have been completed.

If the EC formalizes a joint scientific advice process, Bouvy said, it would eliminate the lack of alignment between regulators, HTA bodies and payers that “too often leads to an unrealistic multiplicity of demands in terms of clinical and real world evidence studies industry cannot deliver on, and unnecessary duplication of work.”

Differences will and should remain between bodies with different remits, he said, but “evidence requirements must be kept realistic and a pragmatic approach must be taken to uncertainty when data gaps exist.”

While EFPIA and EUnetHTA’s joint efforts may simplify demands for evidence across Europe and shorten the time to reimbursement decisions, they intentionally do not address how benefit relative to SOC should be valued or reimbursed. EFPIA contends this must be decided at the national level.

Industry must take a seat at the negotiating table, as well as tapping into efforts

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ECHOUTCOME: Challenging QALYs

Government-industry negotiations over value-based pricing in the U.K. have given the industry an opportunity to supplant or at least supplement QALYs with metrics that do a better job of measuring value.

There’s broad agreement that QALYs aren’t perfect. Even their strongest supporters basically argue they are better than nothing.

In January, a consortium led by biostatistics company **Data Mining International S.A.** argued the metric is “dangerously flawed” and should be dropped.

According to the **European Consortium in Healthcare Outcomes and Cost-Benefit research (ECHOUTCOME)**, four assumptions underlying QALYs are invalid: quality of life can be measured in consistent

intervals; life years and QOL are linked; people are neutral about risk; and willingness to sacrifice life years is constant over time.

The conclusion was based on a survey of 1,300 Europeans. ECHOUTCOME includes French and Belgian academics and is funded under the EU’s Seventh Framework Program (FP7).

NICE Chief Executive Andrew Dillon defended the QALY in a statement: “We need to use a measure that can be applied fairly across all diseases and conditions. The QALY is the best measure anyone has yet devised to enable us to do this.”

However, NICE does not compare the cost per QALY of drugs across different disease settings, nor does the **National**

Health Service (NHS).

ECHOUTCOME proposed alternatives including a simple cost-benefit analysis comparing the cost of therapy versus the costs of no treatment, or a cost-effectiveness analysis expressed as cost per clinical outcome.

Paul Kind, professor of health outcome measurement at **Leeds University**, has proposed a coverage with evidence development scheme in which the NHS would reimburse a new drug for an initial three-year period, during which data on outcomes, side effects and QOL could be collected. Resulting data would form the basis for negotiating a value-based price (see *BioCentury*, March 11).

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by patient groups and academics that seek to improve the metrics used to establish value (see “ECHOOUTCOME: Challenging QALYs,” A11).

An example comes from the U.K., where the **Association of the British Pharmaceutical Industry (ABPI)** and the **U.K. Department of Health** are negotiating the terms of the country’s proposed value-based pricing (VBP) system, which is slated to take effect in January 2014 (see *BioCentury*, March 11).

Both parties are keeping the negotiations under wraps, but documents released by both sides suggest one of the topics on the table is how value will be assessed.

In 2011, ABPI argued that NICE’s methodologies for assessing value — QALYs and direct medical costs — are inadequate to capture the range of benefits drugs can provide to patients.

Among other shortcomings, according to ABPI, the instrument used to quantify health gains for the purpose of generating QALYs — the EQ-5D questionnaire — is insensitive to gains that patients value in certain diseases.

The trade group said industry and government should agree on better methods and metrics but did not propose specific alternatives.

ABPI also said value-based pricing needs to recognize and reward a continuum of innovation that encompasses both incremental and breakthrough products (see “Layer by Layer”).

“An appropriate level of granularity will be required in any sliding measurement scale which will need to be applied to the dimensions of innovation, including those which cannot be valued as part of the QALY,” the trade group wrote.

In June, the U.K.’s Department of Health gave NICE a “blueprint” for determining the value of a drug under VBP. DoH did not disclose details but said the blueprint is a framework for NICE to consider the benefit to patients and the “wider societal benefit,” including the impact the drug can have on a person’s “ability to work or contribute to the economy and society.”

The extent to which patients will participate in developing or implementing VBP is unclear. In March, negotiations over VBP and a new Pharmaceutical Price Regulation Scheme (PPRS) were separated due to a campaign by a coalition of 15 cancer charities that want a seat at the negotiating table

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Layer by layer

The need for incremental innovation is something that has been almost entirely lost in the debate over the role of drugs in healthcare. Indeed, it is ironic to hear those who claim to speak for patients complain about the proliferation of drugs in a particular class, which gives doctors and patients better risk-benefit options.

As of last week, FDA had granted 25 breakthrough designations, and 26 more were pending (see “Breakthrough Bolus,” A6).

Society demands these breakthroughs. But it also is crucial to remember that incremental benefits added together over time are frequently keys to long-term improvements in outcomes.

For example, the **Association of the British Pharmaceutical Industry (ABPI)** has compiled data showing that since 5-FU became available to treat colorectal cancer in 2000, stepwise iterations in treatment that each built upon previous findings have cumulatively doubled OS from one to two years, even though each iteration increased median OS by just a few weeks or months (see “Incremental Innovation”).

Physicians and patients also need to have choices within a given drug class, because

patients frequently have differential responses in terms of both efficacy and safety to different members of a class.

It is also a fact of life that despite industry’s best efforts, many if not most attempts at breakthroughs will not yield step-changes in care.

Thus while most debate today focuses on the need to incentivize development of breakthrough drugs, it remains important to enable incremental improvements.

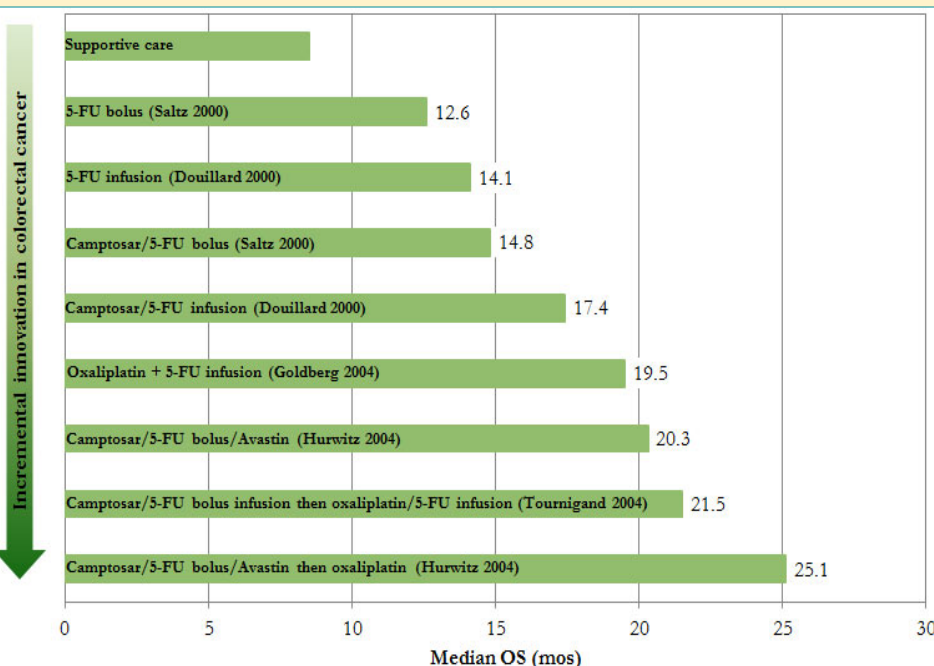
To make this work, the drug industry will be challenged to put its prices in context of overall outcomes. This may produce some ironies.

While Avastin bevacizumab often is held up as an example of an expensive biotech drug that produces a little benefit — 5.5 months of OS in the ABPI example — the **Genentech Inc.** drug was the benchmark for doctors at **Memorial Sloan-Kettering Cancer Center**, who complained that **Sanofi’s** Zaltrap for metastatic colorectal cancer was overpriced without providing better results.

— Susan Schaeffer

Incremental innovation

Between 2000 and 2004, stepwise iterations in treatment, each building upon previous findings, cumulatively doubled median overall survival in colorectal cancer, even though each individual iteration increased median OS by only 0.7-3.6 months. Source: Association of the British Pharmaceutical Industry, 2009



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for VBP (see *BioCentury*, March 11).

Mary Frampton, a spokesperson for **Prostate Cancer UK**, told *BioCentury* that since then her organization and other patient groups have met with senior staff at DoH. She said Prostate Cancer UK also is on a NICE working group involved in determining how drug appraisals will be done under the new system, but the charity remains “frustrated about the level of patient group involvement in the development of the value-based pricing system.”

ABPI spokesperson Andrew Bolan said the trade group “has discussed value-based pricing with patient organizations both individually and as a group on a number of occasions,” including at ABPI’s Patient Organisation Forum in February.

Back to School for 2013 already has argued that disease-focused multistakeholder meetings would be an appropriate venue for developing tools to identify the gains that should be part of a value assessment, as well as the means to measure them. But follow-through will be required.

It will then be incumbent upon drug

developers to include patient- and payer-focused endpoints and analyses in clinical trials, and agree to use the results as the basis for determining reimbursement.

Bitter medicine

Drug companies will have to charge lower prices for many drugs and engage with payers and patients in developing a new consensus on value for money.

It is inescapable that the drug industry’s pricing power is in retreat. Governments, commercial insurers and patients cannot continue to pay tens or hundreds of thousands of dollars for treatments that in many cases provide modest benefits, let alone afford cures that more often than not will come from cocktails of drugs.

On the flip side, both society and the drug industry need to find a consensus on how to price and reimburse for medicines that provide incremental benefits to patients who do not respond to alternative therapies.

Managements and boards have a fiduciary duty to maximize returns to shareholders. But the short-term thinking this mindset typically engenders ultimately will

be value-destroying.

In the short term, the trade-offs for high prices, especially for drugs that contribute modestly to health outcomes, are poor formulary placement, or none at all; requirements for prior authorization; and step therapy.

Back to School is not claiming there is no opportunity for premium-priced drugs, just that the hurdles for any drug to receive premium pricing are going to get very much higher — and the actual prices of even the most effective drugs will fall below the industry’s historical norms.

Managements must come to terms with this reality, as well as the fact that the solutions simply may be incompatible with the demands of current shareholders. Yield-seeking investors may want the biggest companies to keep generating mountains of cash to return in dividends and stock buybacks. But there are limits on what managements can accomplish for shareholders in an era of global austerity.

Oral entrants into the multiple sclerosis space may already recognize the reality, even though these drugs are expected to improve adherence and appear to have

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Linness: Pricing for the masses

Ironwood Pharmaceuticals Inc., its investors and its partner concluded that in the U.S., pricing Linness linaclotide to maximize access was the best route to driving use and generating returns.

Linness is approved to treat adults with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). It is the only IBS-C drug with reduction in abdominal pain in its label.

That benefit easily could have put Ironwood in a position to come to market at a premium to the only other prescription drug for constipation, Amitiza lubiprostone from **Sucampo Pharmaceuticals Inc.** and **Takeda Pharmaceutical Co. Ltd.** Many analysts had expected that.

But Ironwood concluded that while a higher price might look good in the short term, it would likely limit access — and sales — over the long term.

“If we could make the drug available with as few access hurdles as possible, we and shareholders would be rewarded over time in terms of the volume of adult patients we could treat,” CEO Peter Hecht told *BioCentury*.

Ironwood set the wholesale acquisition cost (WAC) of Linness at \$7.10 per day — below the \$8.23 per day for Amitiza.

The company developed its pricing strategy based on extensive conversations with payers, as well as independent research on pricing elasticity from the payer and provider perspective and market research using a blinded product profile.

“We really tried to approach it as though it was not an opinion but rather a data-driven decision,” said Thomas McCourt, CCO and SVP of marketing and sales.

Hecht said it was not hard to get investors on board. “A lot had done their own pricing research and analysis,” he said.

McCourt, who launched constipation drug Zelnorm tegaserod at **Novartis AG**, joined Ironwood in 2009, after the Linness Phase IIb data were in. But Ironwood already had begun to get informal feedback from payers with the Phase IIa data.

As soon as **FDA** approved the label, Ironwood and the managed care team from partner **Forest Laboratories Inc.** went to the marketplace to speed reimbursement decisions.

The guanylate cyclase C (GCC; GUCY2C)

agonist has a novel mechanism. But the selling proposition is the effect on abdominal pain, the symptom that drives IBS-C patients to seek care.

“We made sure all the constituents understood we had an agent that could help relieve abdominal pain associated with IBS-C, not another laxative,” said Hecht.

Forest reported Linness net product sales of \$28.8 million in 2Q13.

As of June, about 80% of commercially insured patients had unrestricted access to Linness, and about 50% have a \$30 co-pay. The company is providing co-pay assistance as a “bridging strategy” until it can get the remaining payers to the table to discuss preferential formulary placement.

“We are tracking where Zelnorm was at this stage,” McCourt told *BioCentury*.

In 2006, Zelnorm had sales of \$561 million after five years of promotion. Novartis withdrew it in 2007 after a *post hoc* analysis of clinical trial data suggested an increased risk of cardiovascular adverse events (see *BioCentury*, July 30, 2007).

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slightly better efficacy compared with injectable standard of care.

The monthly average wholesale price (AWP) of the three newest drugs range from \$4,154 for Sanofi's Aubagio teriflunomide to \$5,562 for Novartis' Gilenya fingolimod, with **Biogen Idec Inc.**'s Tecfidera dimethyl fumarate in the middle at \$5,400. The injectables range from \$4,697 to \$5,525 (see *BioCentury*, June 10).

Even so some of the 2013 formularies for **Catamaran Corp.** required prior authorization for Gilenya, while others listed Gilenya, Aubagio and Tecfidera as non-preferred medications and injectables as preferred.

Catamaran operates across the U.S. and is the fourth largest pharmacy benefits manager (PBM) by prescription volume. It serves large and mid-cap employers, third-party administrators, health plans, Medicaid and state and local government plans.

Back to School argues that industry increasingly has no choice but to engage in real-time experiments that are "price-seeking" rather than "price-setting."

Some of these experiments will fail. But if conducted with rigor and the cooperation of all stakeholders, even the failures should get industry and society closer to models that work.

For example, **Ironwood Pharmaceuticals Inc.** decided its constipation drug Linzess linaclotide needed to be priced to maximize patient access and reduce reimbursement hurdles.

Ironwood priced Linzess at a discount to the only other prescription drug for constipation even though Linzess is the first drug to clearly demonstrate a reduction in abdominal pain. The company's reasoning was simple: the lower the hurdles, the more patients it could treat and the higher its sales would be.

As a result of its pricing decision and extensive upfront work with payers, as of June, about 80% of adult irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC) pa-

tients with commercial insurance had unrestricted access to Linzess — meaning the drug is on formulary with no requirement for prior authorization or step therapy. About half of these patients have a co-pay of about \$30 per month (see "Linzess: Pricing for the Masses," A13).

Another approach is to build pricing and reimbursement schemes that have an adaptive component, one in which a drug's price or reimbursement rate will increase — or decrease — as real-world evidence sheds new light on a drug's benefits, risks and economic impact.

uniQure B.V. and partner **Chiesi Farmaceutici S.p.A.** are considering variations on adaptive pricing as they discuss the potentially curative ultra-Orphan drug Glybera alipogene tiparvovec with European payers (see "Glybera: Pricing for the Rare").

Obviously, variations on adaptive pricing and reimbursement already are being tried around the world, including coverage with evidence development, pay for performance and outcomes-based con-

See next page

Glybera: Pricing for the rare

uniQure B.V. is navigating uncharted waters as it weighs options for pricing an ultra-Orphan therapy that is administered only once and may offer a cure.

In November 2012, **EMA** approved Glybera alipogene tiparvovec to treat lipoprotein lipase deficiency. Glybera is an adeno-associated virus (AAV) vector encoding the LPL gene.

LPL deficiency is an autosomal recessive disorder that affects about one in 1 million people. It is characterized by severe hypertriglyceridemia leading to acute pancreatitis.

The disease is managed primarily by severely restricting dietary fat. Patients who do not manage their diet have an increased risk of mortality.

According to uniQure CCO Hans Christian Rohde, lipid-lowering drugs such as fibrates or statins are also typically used but are generally not effective.

In November, CEO Joern Aldag told BioCentury the company was thinking about a price around €250,000 (\$322,625) per year for the "duration of clinical benefit."

The company has five years of data, which show a persistent clinical effect fol-

lowing a one-time series of injections administered over a few hours.

Over five years, that price would translate into a cost of about €1.3 million (\$1.6 million).

However, last month Rohde said uniQure and European partner **Chiesi Farmaceutici S.p.A.** have not settled on the price. They are discussing multiple pricing schemes with EU national authorities.

Rohde told BioCentury a simple upfront payment is most straightforward and would build a return on investment faster. But he said payers could balk at a very high upfront price if they don't think the available long-term data are sufficient.

Rohde noted even an upfront payment isn't that simple because the number of injections needed depends on a patient's weight.

Price volume agreements could be considered, such as rebates if total cost of the therapy exceed a certain threshold, he said.

Rohde said an annuity payment structure might make revenues more predictable over time. This scenario could entail charging about half the price at time of administration, followed by annual payments of 10-

20% over subsequent years.

The number of years over which the annuity would be paid would "likely depend on how many years of data you have," he said.

The risk management plan uniQure agreed to with EMA includes a 15-year patient registry, which would give the company about 20 years of data.

A variation on the annuity scheme could be a risk-sharing agreement that makes use of the registry. Rohde said this scenario would likely include a partial upfront payment and annuity payments linked to the patient's response to treatment and compliance with dietary restrictions, which must continue even after treatment with Glybera.

"You need to be sure that the patient follows this diet, because if patients don't do that or start drinking alcohol, there is of course a risk that you will get a pancreatitis event," Rohde said. "And then the authorities might say this drug doesn't work."

uniQure and Chiesi expect to launch Glybera in Europe in 1H14.

— Stephen Hansen

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tracting. Since these experiments will go on with or without industry's participation, drug companies can only lose if they refuse to play.

Indeed, the drug industry must be seeking to shape how key parameters of these schemes are defined. Companies need to be actively engaged in identifying the appropriate benchmarks for drug performance, establishing the length of time over which to measure them, determining who should collect the data and establishing the consequences of different results up front.

These scenarios also will require companies to play a bigger role in ensuring the appropriate use of their medicines.

One example is the recent trend toward outcomes-based contracting in the U.S. Most of these deals include traditional risk-sharing features similar to those first seen with NICE: if a drug does not improve outcomes when used properly, then the company agrees to share costs with payers and patients through refunds, increased rebates or increased discounts.

The newer deals add more wrinkles, among them extra payments from drug companies to payers if patient adherence rates improve or reach a predetermined threshold.

While this sounds counterintuitive, the idea is that increased adherence will raise drug volumes for manufacturers while

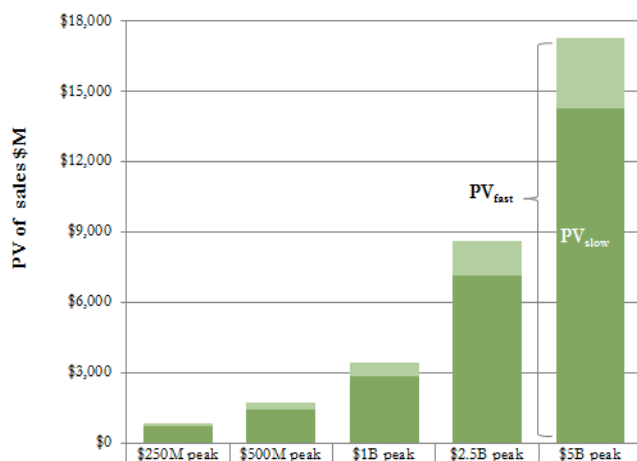
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Launch limits

Investors are already factoring in slower launch trajectories due to payer pressures, in some cases modeling peak sales 7-8 years from launch rather than 3-4 years. This can significantly reduce the value of a drug. Assuming a 20% discount rate and a launch in 2014, the present value of the revenue stream for a \$1 billion drug drops by \$592 million, or 17%, to \$2.9 billion, if the peak is reached in 2020 rather than 2017.

For a drug with \$5 billion in peak sales, the PV drops by \$3 billion (17%) to \$14.3 billion, while the PV of a drug with \$250 million in peak sales drops by \$148 million (17%) to \$715 million.

The model below assumes 14 years of market exclusivity, and a terminal value based on 10% of peak sales and no growth assigned thereafter. PV_{fast} = PV of a drug's sales peaking in 2017; PV_{slow} = PV of a drug's sales peaking in 2020; \$M



Diff PV[fast] vs. PV[slow]	\$148	\$296	\$592	\$1,479	\$2,958
PV[slow]	\$715	\$1,430	\$2,860	\$7,150	\$14,300

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BioCentury's mission is to provide value-added business information & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

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simultaneously improving outcomes for patients and reducing payer costs (see *BioCentury*, May 14, 2012).

Tying price and reimbursement to outcomes also calls for a greater shift from counting the number of sales rep calls to working with customers to improve care in ways that extend beyond drug therapy.

For example, providing patient care services is already standard operating procedure in the rare disease space and in MS, and there are experiments ongoing in areas such as diabetes and addiction (see “*Suboxone: Selling with Service*”).

However, it is important to understand that these services simply will add to the cost of doing business, even if they shore up reimbursement and increase product sales.

Indeed, as pricing power erodes, demands for evidence increase and sales ramps lengthen, margins and the expected lifetime value of a product are simultaneously going to shrink.

Industry will still be profitable, but drug companies and their investors won't be able to confidently forecast how much profit is possible until these experiments produce a social consensus on value for money.

David Miller, SVP of global market access at Biogen Idec, notes that asset values can plummet when market access is delayed.

Over 20 years, Miller said, he has seen the NPV of a drug drop by as much as half due to a combination of factors: extra money spent to generate evidence; delay in pricing and reimbursement; slower uptake, perhaps including incursion of new entrants; and decreases in assumed pricing, even with new postmarket data.

“If an asset is shut out of pricing and reimbursement while additional evidence is produced, then the asset will lose significant value,” he told *BioCentury*.

Investors agree. They are seeing peak sales pushed back, and point out that a delay to as much as seven or eight years after launch can reduce a drug's PV as much as 17% (see “*Launch Limits*,” A15).

Get to work

Back to School does not suggest the issues around reimbursement and patient access can be fixed overnight. Meeting society's need for new and better drugs at an affordable cost, while ensuring returns for drug developers, will only be resolved

Suboxone: Selling with service

Reckitt Benckiser Group plc provides one of many examples of how a company can address patient and payer problems by offering services alongside drugs.

Reckitt markets sublingual Suboxone buprenorphine/naloxone to treat opioid addiction in the U.S. The company also runs the “Here to Help” program, which is free to patients who take the drug.

The program includes a help line to counsel patients, keep them on the drug and prevent relapse. The help line provides patients with information on addiction counselors in their area.

Reckitt also provides online tools to help patients manage triggers and risky behaviors associated with relapse as well as set goals, track accomplishments and share them with their treatment team.

A post-market study in 826 opioid-dependent patients showed that 78% of patients given Suboxone with Here to Help counseling remained adherent to medica-

tion at six months vs. 64.7% of patients treated with Suboxone but not counseled through the program ($p < 0.001$).

Additionally, 78% of patients who remain adherent at six months reported a reduction in illicit drug use compared to 39.5% of non-adherent patients. No p-value was reported for the latter endpoint.

The program isn't exclusive to one payer or provider group. “There is an enormous benefit that comes along with it,” said Edmund Pezalla, national medical director of pharmacy policy and strategy at **Aetna Inc.**

A 30-day supply of the sublingual film has a wholesale acquisition cost (WAC) of \$211.15.

Aetna and **UnitedHealthcare Group** list the drug as Tier 2, the category for preferred banded drugs above the Tier 1 generics. Monthly co-pays are up to \$50, according to Reckitt's website.

— Erin McCallister

with many experiments. But the reality must be faced.

Without these efforts, industry's reward for creating New Value will be determined by direct and indirect controls on prices and utilization, and other blunt instruments.

Back to School has identified three venues where the drug industry can manage its future.

First, industry should spearhead multistakeholder meetings focused on specific diseases at which patients, payers, companies, researchers and regulators can arrive at a shared understanding of a disease and its manifestations and a consensus on how to measure outcomes.

Second, industry should pursue opportunities to develop evidence of value creation through partnerships with healthcare providers whose business models now require them to demonstrate improvements in the quality of care they deliver. Integrated health systems and ACOs top the list, along with Medicare

Advantage providers, hospitals and large physician groups.

Third, industry should ramp up efforts to be at the table wherever health technology assessment takes place in the U.S., Europe and the rest of the world.

A fourth recommendation is less about action than attitude: The drug industry must come to grips with the fact that it cannot reverse the course of falling drug prices. And clinging to old attitudes will prevent success on the other three fronts. Simply put, no one will work with an industry that looks to be profiteering.

So the experiments with unfamiliar, even hostile, collaborators will have to take place.

These engagements will reveal opportunities where drug companies can provide products that are differentiated in ways that change patient lives, solve payer problems and are therefore worth paying for.

Real collaboration with payers and patients also will amass a trove of information that will be used to improve trial designs and to develop evidence that drug companies can use to prove the benefits their products deliver.

These projects will develop a menu of pricing and reimbursement policies that marry price with value, that are flexible

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The experiments with unfamiliar, even hostile, collaborators will have to take place.

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enough to accommodate incremental as well as breakthrough innovation, and that drive revenues and profits by extending access and adherence to a bigger pool of patients.

Many of these experiments will fail. But over time they will lay the groundwork for a new framework where drug developers and their investors can more reliably predict their return on investment.

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