Game's Up, Pharma: The New Drug Pricing Dynamics

Hepatitis C drugs may have provided the spark, but cost-pressured payors, empowered consumers, and at-risk providers are adding fuel to the drug pricing fire. The game may be up for pharma firms that try to push prices out of line with perceived value, potential patient volumes, and affordability.

BY MELANIE SENIOR

- The hepatitis C market has shown what more aggressive payors and strong competition can do to drug prices.
- It's unlikely to be a one-off: as the cost of specialty drugs rises, so those paying will seek to squeeze out better deals.
- That includes increasingly empowered consumers, incented by higher out-of-pocket costs to shop around. Biosimilars will provide further pressure on pricing in some categories, though how far or fast isn't clear.
- Pharma's days of pricing at will are limited to clearly differentiated products, with no competition.

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Eighteen months after **Gilead Sciences Inc.** launched hepatitis C drug *Sovaldi* (sofosbuvir) at an eye-popping $84,000 per 12-week treatment course, Sovaldi has now become synonymous with a debate over drug pricing that continues to rage. But the story is no longer about the $1000-per-pill launch price of Sovaldi in the US. It's now about how fast and furiously the cost of this medicine, and others like it, has fallen since.

Sovaldi's launch didn't by itself build the drug pricing fire; it simply provided the spark. The rising cost – and number – of high-priced specialty drugs more broadly, combined with the effects of the 2010 US Affordable Care Act, had already created the conditions for a pricing showdown: at-risk providers, cost-pressured payors, and a growing number of increasingly empowered health care consumers facing higher co-pays and thus with more incentive to shop around. Sovaldi and the rapid succession of competitors behind it provided large pharmacy benefit managers (PBMs) such as **Express Scripts Inc.** the perfect opportunity to turn the screw and show that they were prepared to say "no" to a new drug.

This wasn't the first time a payor had balked: in 2012, the **Memorial Sloan-Kettering Cancer Center** snubbed **Sanofi**'s colorectal cancer drug *Zaltrap* (ziv-aflibercept), prompting a 50% discount. In that case, though, it was the drug's questionable added benefit that prompted the price cut. Sovaldi's effectiveness is undisputed. Here (with far larger sums at stake), it was about market competition. Express Scripts' stance set in motion discounting that was unprecedented in its speed and aggression. The PBM in December 2014 agreed to make **AbbVie Inc.**'s newly approved hepatitis C treatment *Viekira Pak* (ombitasvir/paritaprevir/ritonavir/dasabuvir) first choice for most patients in exchange for a significant discount. That in turn led Gilead to secure preferential positioning – via discounting – for its follow-on treatment *Harvoni* (sofosbuvir plus ledipasvir) with **CVS Health Corp.** and **Anthem Inc.**, respectively a large PBM and

managed health company. (*See "The Price War On Drugs: HCV Competition Finally Sparks Discounting"* — IN VIVO, *January 2015*.) Other deals followed. The end result, according to Gilead in its 2015 guidance to analysts: an average 46% discount for Sovaldi and Harvoni (the difference between gross and net pricing) just months after Harvoni's launch. (*See "Gilead Expects Fewer Payer Restrictions In 2015, Says 250,000 Could Be Treated In U.S."* — "The Pink Sheet" DAILY, *February 3, 2015*.) And the money-off deals are spreading: **Prime Therapeutics LLC** in January 2015 declared that it was most cost-effective to cover both drugs at the prices offered, rather than agreeing to an exclusive deal on either.

These dynamics aren't dissimilar to the steep generic-driven price drops still facing many Big Pharmas in the small-molecule space. "This is sounding not unlike a generic strategy," comments Roger Longman, CEO of **Real Endpoints LLC**, a reimbursement-focused health care analytics company. Granted, hepatitis C has some unique characteristics: Sovaldi arrived as a convenient, orally available cure for many patients, thus with full, specialty-style pricing power in a therapy area that's relatively large. The cost implications for payors were therefore huge, exacerbated by the timing of Gilead's launch of the drug, which came, awkwardly, after many payors had completed budgetary planning for the year ahead.

But few believe that Sovaldi is a one-off. Payor muscle-flexing triggered by a hefty launch price and rapid succession of look-alike drugs will likely spread across other therapy areas. CVS Health is already setting up for battle in another new product category, the cholesterol-lowering PCSK9 inhibitors. (*See "Formulary Focus: PCSK9 Drug Prices May Lead Payers To Impose Coverage Restrictions"* — "The Pink Sheet," *January 26, 2015*.) It has warned that these drugs may cost the health system $150 billion a year, given the huge potential patient population of up to 15 million (five times more than in hepatitis C). Yet here too, there's fierce competition: Sanofi and partner **Regeneron Pharmaceuticals Inc.**, armed with a priority-review voucher, recently leapfrogged **Amgen Inc.** at FDA with alirocumab (proposed name *Praluent*), whose review deadline is July 24. Amgen's evolocumab deadline is just weeks later, in late August. Approvals in tight succession will likely force a vigorous fight for preferential positioning among the key PBMs and payors from the outset. Indeed, deals may even be agreed prior to approval: Express Scripts' Steve Miller, SVP and chief medical officer, hinted on Bloomberg earlier this year that he was already "working with" the PCSK9 sponsors. Further Phase III competition from **Pfizer Inc.**'s bococizumab and earlier candidates will only exacerbate the price-driven fight.

What are the implications for how pharma prices new drugs? Certainly, launch list prices for the first-in-class candidates won't go down; it's reasonable to assume they may even rise further, given the curtailed period during which manufacturer can expect to maintain that price before competition arrives. "We see no feasible means by which either public or commercial payors will put effective pressure on the launch prices of new specialty products," wrote analysts at Sector & Sovereign Research in 2014.

But overall, net prices will erode faster as payors exploit competitive dynamics to extract discounts. They may even seek to create competition in categories where technically none exists, for instance by promoting off-label use of a particular drug in a certain setting where, say, only one has labeled approval. "The notion that you'll be the only drug in a particular category … it's great for the time you're there, but will drive more interest in creating competition, by whatever means," predicts Real Endpoints' Longman.

PBMS DRIVE DISCOUNTS, BUT WHO BENEFITS?

A 30% to 40% drop in the cost of a curative drug within just months sounds like a good thing for all involved: payors, providers, and, most significantly, patients. Out-of-pocket drug costs for individuals are rising fast, with co-pay percentages inflating on specialist drugs in particular, as payors try to deal with the growing number of these high-priced products. "Anywhere from 30% to 50% of the total drug spend is now on specialty drugs," warns Harry Travis, VP of specialty and home delivery pharmacy at **Aetna Inc.**, yet they're consumed by less than 5% of patients. And it only looks set to get worse as more and more new drugs fall into the "specialty" category (loosely defined as those costing more than $600 per month, and often many times more).

But the US health care system isn't straightforward. It involves a host of different players, with differing incentives, each seeking to make profits on a different part of the chain from manufacturer to patient. Sovaldi and the broader changes wrought by the US ACA have begun to shine a spotlight on the complex, sometimes conflicted role of large PBMs like Express Scripts, CVS Health Corp.'s CVS Caremark, or Prime Therapeutics.

On the one hand, these players have been instrumental in forcing the sizeable discounts seen in hepatitis C. The market share they command, and resulting power they have to influence drug uptake, means manufacturers will bend over backward to win favorable formulary positioning. "Absent our move, Gilead was not going to offer anyone new [discounted] contracts," contends Express Scripts' Miller. "We opened up the hepatitis C market places … generating billions of dollars of savings." Miller claims that Express Scripts was simply pulling the lever of the free market to counterbalance against the kind of temporary monopoly enjoyed by Gilead for about a year after Sovaldi's late 2013 launch. "This [creating competition and savings] is what we're set up to do … uniquely, on the drug and pharmacy side," he argues.

It suits Express Scripts to portray itself as saving costs, and to persuade its customers – health plans, providers, employers – that it's offering the best deals. And there's no question that its aggressive moves have cut a path for other, smaller PBMs to benefit from similar discounts on the same drug, which they may not have had the power to win on their own.

But it's not always clear that the discounts PBMs (and other intermediaries, such as wholesalers or drug retailers) extract from manufacturers are passed downstream to payor-providers and ultimately to patients. "When prices fall [due to discounts, as was the case in hepatitis C] the vast majority of those savings benefit the PBMs, rather than the payors," contends Bryan Birch, CEO of **Truveris Inc.**, whose products help make PBMs' offerings more transparent and easily comparable. Birch acknowledges, though, that the extent to which discounts are shared depends hugely on the PBM and on individual stakeholder contracts.

Meanwhile, manufacturers often pay back rebates to PBMs or plans (including within Medicare), as a portion of overall spend on

a particular drug or group of drugs. These are coming under growing scrutiny amid ACA-triggered changes. Rebates often comprise a very profitable part of PBMs' businesses. In principle, they can help cut costs, since PBMs and insurers can demand higher rebates on me-too and older drugs to keep them on formulary. But they can also incent price increases rather than price falls, because they're calculated as a percentage of overall sales. This can range from 5% to as much as 50%, according to consulting firm ZS Associates. And if health plans or PBMs try to extract higher rebates, manufacturers may simply raise their prices to compensate.

High-margin specialty drugs are likely to face more rebates under Medicare Parts A and B, according to analysts at Sector & Sovereign Research; commercial formulary managers will likely demand rebates on such products, too, given the growth of more restrictive health plans with higher cost-sharing (making it harder to promote uptake of such products).

Given these complex, opaque dynamics, many experts feel that rebating (worth about $40 billion a year, according to ZS Associates) is hurting US health care spend. Real Endpoints' Longman predicts that "the rebate issue will come back to haunt them [PBMs]."

Already, though, a host of newer players like Truveris and other health benefits managers have emerged to help payors, employers, and providers better understand and control the downstream costs and implications of favoring one particular drug over another. In the post-ACA world focused on outcome and overall costs, not simply drug spend, they're demanding more transparency and ultimately may seek to curb PBMs' control over drug formularies. "We ferret out the best deal on the long-term basis for our clients," sums up Birch, including with products such as *RxChoice* that provides easy-to-compare online quotes from PBMs. "Any time you have a free market, led by capitalism, you'll try to drive up profit until there are further entrants in the market, or tools to evaluate fair profitability," he says.

PATIENT POWER SHOULD PUSH PRICE TRANSPARENCY

The growing drug cost burden on patients will also drive more transparent pricing. Health reform compels more individuals to buy insurance, but the skyrocketing price (and number) of specialist drugs, is pushing a growing portion of health plans to charge patients 30% or more of the cost of those drugs, according to a study by Washington, DC-based advisory firm Avalere Health. And although these products are consumed by a minority of patients (causing serious imbalances in costs across the population as a whole), they're used to treat an ever-wider range of serious, often chronic conditions including rheumatoid arthritis, multiple sclerosis, and certain cancers.

Heftier personal bills is having the immediate-term effect of compelling pharmaceutical firms to engage in more co-pay assistance programs (co-pay cards), eating into net sales and ultimately incenting plans to increase out-of-pocket costs even further. The longer-term effect of more burdensome out-of-pocket costs is to prompt patients to shop around. That trend alone will vastly change the overall industry, predicts Birch. "More member liability means more power in consumers' hands, which demands transparency so they can ensure they get the value they need at point of sale," he says. The result may eventually be that individuals start to purchase directly the drug that their physician has recommended, bypassing the middlemen. "Decision making may shift from business entities to individuals," speculates Birch.

We're not yet at an Amazon-style market for prescription drugs; regulatory constraints may preclude that ever happening. But the balance of pricing power, having already shifted away from manufacturers toward large PBMs and payors, may well soon shift further toward providers and patients, as both groups seek to take more control over what drugs they buy and at what price.

BIOSIMILARS: CRUCIAL TO THE AFFORDABILITY OF HEALTH CARE?

Meanwhile, biosimilars' long-awaited arrival onto the US market should provide further downward pricing pressure and more choice across multiple therapy areas. Citing potential savings worth $250 billion over the next decade – way more than those savings recently extracted in hepatitis C – Express Scripts' Miller declares that biosimilars are "crucial for the affordability of health care in the US." For Aetna's Travis, copycat biologics are the "number one tool we will have to control growth of specialty drug spend." Because industry's pipeline continues to fill with biologics – 71% of the top 10 best-sellers in 2012 were biologics, according to Tufts Center for the Study of Drug Development – biosimilars "will be a long-term trend," Travis contends, providing pricing pressure on a wide range of both new and older biologics.

Payors describe biosimilars as providing much-needed budgetary relief that will in turn allow newer drugs to be paid for. (This pro-innovation stance, as well as looking good, also conveniently keeps the door open for rebates on innovator drugs.) But how fast that relief will be realized, and how significant it will be, is far from clear. On March 6, FDA granted its first approval under the abbreviated 351(k) pathway: **Novartis AG/Sandoz Inc.**'s *Zarxio* (filgrastim-sndz), a biosimilar of Amgen's *Neupogen*. (*See "Now Comes The Hard Part: Sandoz Must Sell Its Biosimilar"* — "The Pink Sheet," *March 9, 2015*.)

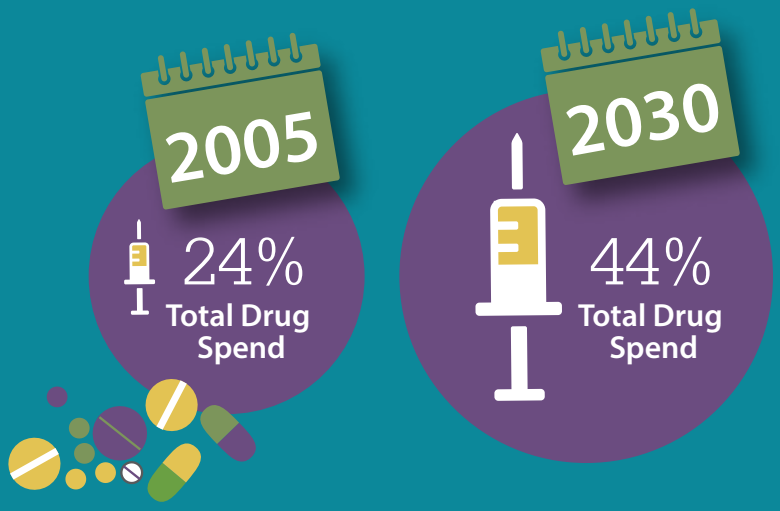
> "Biosimilars are the number one tool we will have to control growth of the specialty drug spend." – Harry Travis, Aetna

A handful of other products are under review, but this dearth of biosimilar approvals in the US, nine years after such products launched in Europe, reflects innovators' extraordinarily effective defense tactics. Those will continue as biosimilars reach the market, including via information campaigns that raise doubt over the copycats' degree of similarity to the originator drugs.

Biosimilars face two further brakes on uptake: as seen for pioneer Zarxio, most will have non-proprietary names (INNs) distinct from their reference drugs, and won't be labeled interchangeable, at least for a time. In sum, "there are far more hurdles" to extracting savings from biosimilars than there were in hepatitis C, acknowledges Express Scripts' Miller.

He claims Express Scripts has been working to prepare the ground for biosimilars for several years, including via educational outreach to pharmacy groups. The PBM says

Rocketing US specialty drug spend



7 of 10

Top selling drugs will be specialty products within 4 years

Burgeoning specialty drug pipeline and approvals

Of drugs in development (650 in total) are specialty

19 of 39

New entities approved by the FDA in 2014 were specialty, mostly in oncology and rare diseases

51%

Of specialty drug spend covers products in cancer, RA and MS

New drugs expected to be approved in US near term will be specialty

Growing consumer costs

60%

Of lower-premium 'bronze' health plans demand more than 30% of cost of (pharmacy benefit) drugs from consumers

5% of employer plans utilized specialty 'tier' charging consumers a % of drug costs

23% of employer plans have specialty tier

SOURCES: Pharmaceutical Care Management Association; Health Affairs; Avalere Health; UnitedHealth Group

it will continue to educate in favor of biosimilars and to collect real-world data to support safe switching to these cheaper products. But trying to prove a negative – that biosimilars don't do any harm – is hard. Until biosimilars are labeled interchangeable – and it's unclear if or when FDA will grant such a designation – biosimilar sponsors will have to offer big discounts to incent payors to bother switching patients over. Not only that, they'll also have to counter the often-hefty innovator drug rebates, which may well be withdrawn if preference is given to a biosimilar competitor. "Whether the PBM or plan gets enough market share onto the biosimilar to ensure the discount on the copycat outweighs the lost rebates on the originator is an open question," says Longman.

Biosimilars' impact on US health care costs won't be immediate. For the first handful of products at least, the speed of uptake will be very compound-specific: the relatively simple filgrastim molecule, supported by an experienced, Western sponsor and used in an acute setting across a range of closely related indications, will probably have an easier ride than biosimilar infliximab (**Johnson & Johnson/Merck & Co. Inc.**'s *Remicade*). This complex monoclonal antibody, manufactured by Korean sponsor **Celltrion Inc.**, is used chronically in rheumatoid arthritis but also in gastrointestinal settings such as Crohn's disease. It won approval in Europe, based only on clinical data in the arthritis setting, but even if FDA follows suit, GI specialists in particular are likely to be skeptical. (*See "2015: US Biosimilars' Year of Reckoning"* — IN VIVO, *February 2015*.)

EUROPEAN EXPERIENCE MAY BRING TAILWIND

But if cost pressures continue to mount on both payors and, crucially, patients, even modest US experience with biosimilars may be enough to compel uptake. Clinicians, regulators, and patients may already take comfort from Europe, where several countries that operate nationwide hospital tenders for lowest-price biologics have switched many patients from one product to another, thus far without ill-effects. Norway has embraced biosimilars most avidly, and isn't hesitating to promote the complex antibodies, either: in early 2014 biosimilar infliximab won a national tender with a 39% discount on the branded drug. Norway is taking switching studies into its own hands, too, with the government-funded NOR-SWITCH study designed to reassure clinicians that patients can safety be switched from the brand to the biosimilar.

Biosimilar infliximab, sold in Europe by Celltrion and Hospira (now part of Pfizer) as *Remsima* and *Inflectra*, respectively, is currently being rolled out across larger markets such as France, Germany, and Spain following the February 2015 expiry of a pediatric license extension for Remicade in these countries.

With powerful, often monopolistic national health systems and rigorous health assessment agencies, Europe has long exerted more aggressive price controls than the US. But the growth of high-priced specialty drugs continues to force more extreme measures there, too. As it is, most European countries negotiated prices for Sovaldi that are lower than in the US. France in November 2014 boasted the lowest price across the region (€41,000/$51,000 per 12-week course) plus further volume-linked discounts and a rebate in case of treatment failure. This deal came in part thanks to a selective tax on drug firms whose product costs collectively exceed a certain threshold each year. Four German statutory health insurers in early 2015 declared they'd secured discounts on the drug's €60,000/$67,000 list price in that country, though no details were given. In the UK, Sovaldi costs about £35,000 ($54,000) per 12-week course.

> **"The overall industry will be changed very quickly – in the next three to five years." – Bryan Birch, Truveris**

But Sovaldi's arrival in Europe and the multiple parallel pricing negotiations prompted talk of – and some early efforts toward – international pricing negotiations for new products. Four or five countries negotiating collaboratively will have the leverage to extract far better deals than each separately, given the patient volumes at stake.

European payors won't pay at all for drugs that are deemed too expensive relative to the value they bring. Sovaldi, for all its headlines, was widely deemed cost-effective. England's National Institute of Health and Care Excellence approved it for certain patients during 2014. The problem is affordability, given the number of eligible patients. Access to Sovaldi for many patients in England has been delayed until mid-2015 as regional authorities round up the necessary funds.

Other drugs, in particular for cancer, often don't tick the cost-effectiveness box. Pretty soon that will mean they're simply not available at all, warns UK-based consultant oncologist Karol Sikora, PhD. For the past few years, many cancer drugs in the UK have been funded by a dedicated, £200 million-a-year Cancer Drugs Fund. But that can't last; already, it faces NICE-style restrictions on what it can pay for. "The Cancer Drugs Fund will go after the next [UK general] election" in May 2015, predicts Sikora. Most of the two dozen or so cancer drugs approved by the European Medicines Agency over the last two years are priced in the £60,000 to £100,000 range, making them "simply unaffordable for common cancers," insists Sikora. Particularly as their benefits are relatively limited, he continues, often to a few weeks' or months' of progression-free survival.

There are solutions: more, and more reliable, biomarkers to allow truly personalized treatments; more widespread embrace among pharma of money-back deals if drugs don't work; or, the simplest, reduced prices – perhaps in exchange for higher volumes. Short of these, though, "it's going to end in disaster. Governments, health care providers, and insurers are going to stop funding cancer drugs," warns Sikora.

CONTROLLED DRUG PRICING: A BIG ENOUGH STICK?

There are similarly urgent calls to action on drug pricing in the US. President Obama's proposal in early 2015 that Medicare should have price negotiation powers over Part D drugs may be unlikely to pass through Congress. But the fact that US drug price controls are being talked about at all provides the biggest incentive for all health care stakeholders to allow market forces, including biosimilar competition, to more freely, and transparently, drive prices to the levels that payors and patients can bear, and which more clearly reflect drugs' value.

Quantifying that value isn't easy, not least as it may vary widely by indication, setting,

and indeed by individual patients. There have been attempts in Europe to close in on "value-based pricing," though they have not, as yet, been successful. US experiments around value-based insurance models continue, alongside myriad outcomes-focused set-ups such as medical homes and accountable care organizations. These may eventually help force more value-focused pricing, though they're not designed to do so. Meanwhile, several drug firms have begun to engage in "beyond the pill" services to help ensure their products deliver the promised outcomes, and thus more clearly demonstrate value-for-money. Some firms have committed to limiting price inflation for some existing products.

For now, though, outside of hepatitis C there are few signs of falling prices in the US. And indeed, the premiums on new, differentiated drugs will remain or even grow. But it appears inevitable that the prices of everything else will have to fall. Health care is an industry about to confront consumer-driven market forces similar to those faced by other sectors. "The overall industry will be changed very quickly – in the next three to five years," predicts Truveris' Birch. That will mean game's up for pharma firms pushing prices out of line with perceived value, potential patient volumes, and affordability.

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