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The Shrinking Value Of Best-In-Class And First-In-Class Drugs

by Roger Longman

Incumbency ain't worth what it once was. Pharma companies are spending billions to create advantages that won't have significant lasting power. Smart followers can do as well – for less.

- As payors struggle to control their spend on specialty drugs, they will be less likely to allow best- or first-in-class drugs to gain dominant market shares.
- To do so, they are crafting strategies to restrict physicians from widespread prescribing of new, expensive drugs.
- For pharma, market incumbency will be far more difficult to achieve. Payor-friendly market followers who leverage the groundwork laid by their predecessors could achieve higher ROI.

It's the Planck constant of the pharmaceutical industry: if you're going to build a commercially successful drug, it needs to be either first- and/or best-in-class. Either one can create incumbent market share leaders – and incumbents in drugs, like incumbents in the legislature, are enormously difficult to dislodge. As a consequence, the first/best-in-class principles are used to justify enormous risk and enormous expenditures. They've even created a market for priority review vouchers.

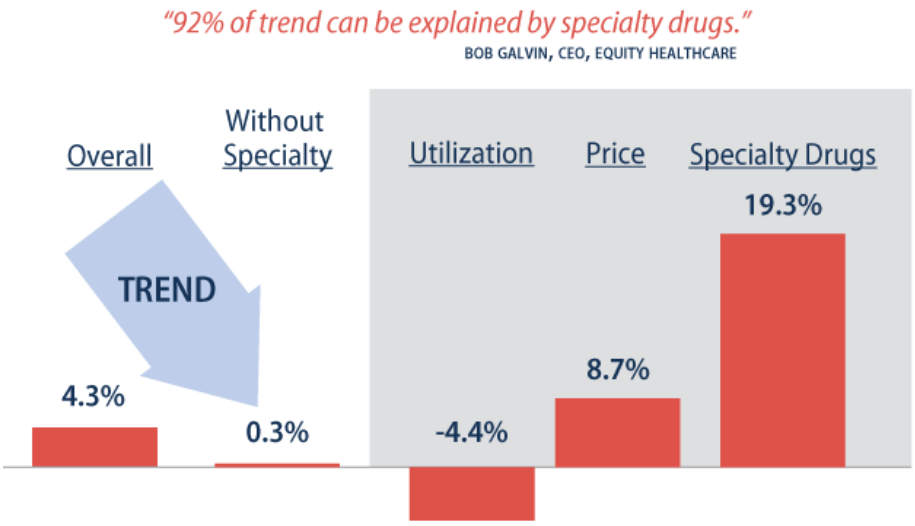
And yet they're becoming less relevant -- or at least relevant for shorter periods of time.

In a world dominated by industrial-style purchasing of health care, pharmaceuticals included, the only viable standard for commercial success will become best *value* in class, defined in apples-to-apples comparisons of efficacy, safety, usability, and economics. Incumbency – a key advantage of which is to maintain price premiums – is in fact a primary target for payors who recognize its costs and who are now gathering more and more of the tools they need to counter it.

Think about drugs from the insurers' point of view. Nearly all of the increase in medical spending is due to the increasing spending on specialty drugs. (*See Exhibits 1 and 2.*) Plans' traditional customers – the employers –are screaming for solutions. Meanwhile, plans' fastest growing and most desirable new customer base – relatively healthy consumers joining through health exchanges or Medicare Advantage plans – base their decisions first and foremost on plan price. And specialty drugs are an increasingly important component of the insurance premium – and for plans, the most unpredictable.

Exhibit 1

Specialty Drugs Driving Cost Increases: Medical Inflation At Equity Healthcare



Based on health spending at Equity Healthcare, a Blackstone company that works with private equity firms and their portfolio companies to manage health care costs, and is therefore a good proxy for a typical large employer.

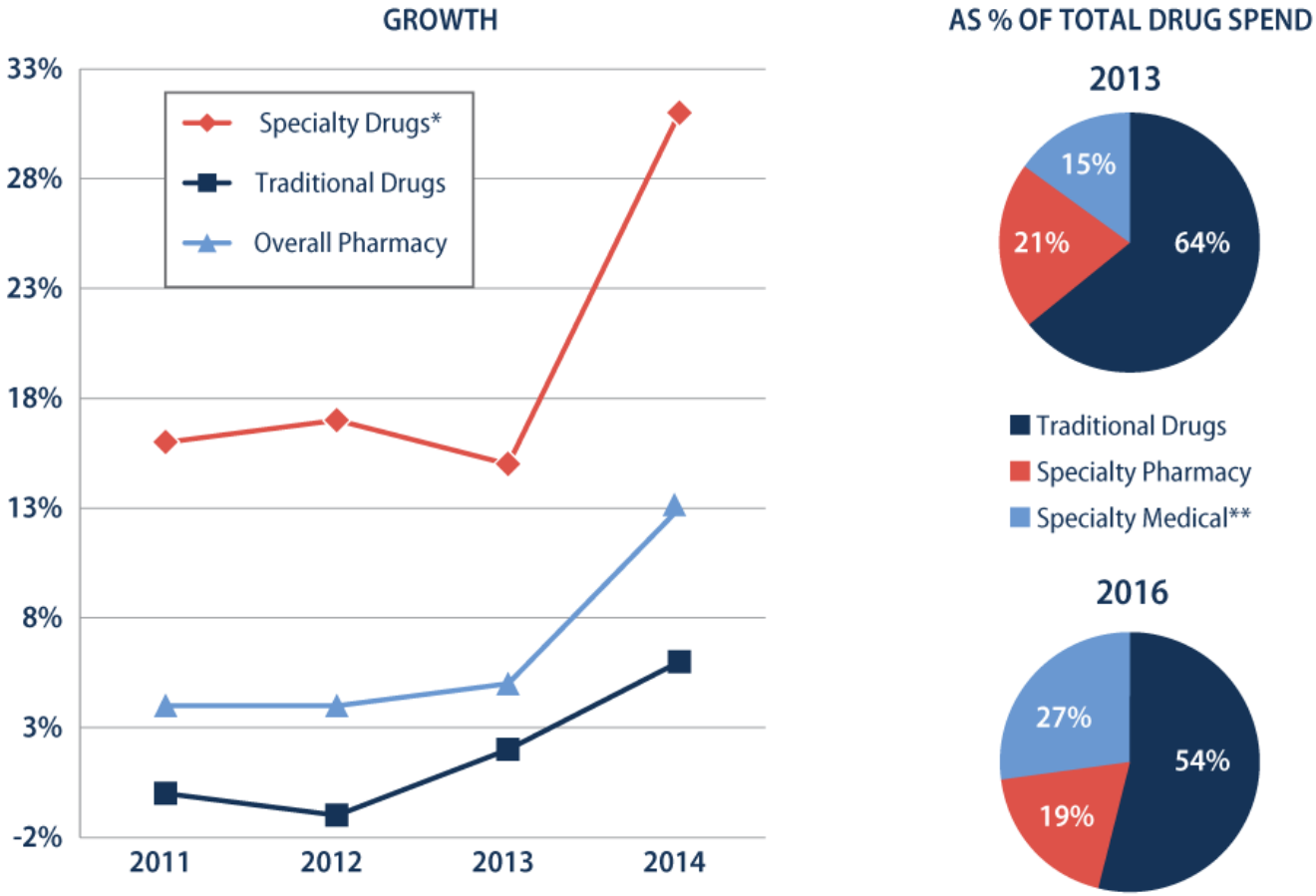
SOURCE: Equity Healthcare

In short, payors need to gain control of their specialty pharmaceutical spend. And to do that they want desperately to counter incumbency in at least two forms – what I'll abbreviate as the *Sovaldi*-first-in-class and *Humira*-best-in-class situations. How do you stop physicians from prescribing new, expensive drugs to many people for whom, plans believe, the drug's benefit may vary – the Sovaldi situation? And how do you avoid the creation of monopolistic pricing power by a compound that is – *at only one point in time* – seen as best-in-class: the Humira situation?

Exhibit 2

Specialty Spend Rising Quickly

Will soon be almost 50% of total drug spend



*Specialty drugs (paid through pharmacy benefit and usually via pharmacy)

** Specialty medical (paid through medical benefit and administered in medical facility)

SOURCE: Express Scripts Drug Trend Report; MarketScan Commercial Database; Express Scripts analysis

Why Plans Hate Incumbency

In the old days – say 24 months ago – a drug with a novel mechanism of action that arrived first on the market could expect to attract the interest, and at least experimental prescribing, of many physicians. Payors would do what they could to make the new drugs more expensive for patients, relegating them to higher reimbursement tiers with higher co-pays.

But, for the most part, these tactics failed. Most payors took a minimum of six months, and often more, to come to any coverage policy decision. And usually the decision was much the same as the initial non-decision: keep the drug on a high tier, but available. Not a problem for drug companies: they simply reimbursed the co-pays for these patients through mechanisms like co-

pay coupons. The drug price certainly covered the incremental expense. A first-in-class drug – at least one that worked well – could thus build a substantial prescribing volume as the drug company companies aggressively marketed its novelty and benefits and physicians rushed to try it.

By the same token, drugs that could demonstrate what their manufacturers, or an economically insensitive market, defined as a best-in-class profile could more than make up for late market entrance. *Pfizer Inc.*'s *Lipitor* (atorvastatin) was one good example – more cholesterol-lowering punch per milligram was enough to impute superiority over *Merck & Co. Inc.*'s *Zocor* (simvastatin). Likewise *AbbVie Inc.*'s TNF inhibitor Humira (adalimumab): it drove to the number one spot in rheumatoid arthritis largely by exploiting a dosing advantage over its earlier-to-market competitors *Enbrel* (*Amgen Inc.*) and the infused *Remicade* (*Johnson & Johnson*), and then by adding new indications.

Humira has been a particularly important cautionary tale for payors – one partly of their own making – and a perfect example of how a once best-in-class drug has been able to dominate a market long after its actual clinical advantage has dimmed. Indeed, Humira, with what is likely to be $14 billion in revenue this year, has been able to raise prices annually, at double-digit rates, with almost no dent in its market share, because it has become virtually impervious to competitive assault (and will remain so until the basic facts of this market change – which they're likely to do with the introduction of biosimilars).

The first reason: physicians don't want to switch stabilized patients off current therapy to different drugs – even if those drugs are significantly cheaper. Doctors figure that switching is just not worth the risk. And because most of those patients are on Humira, AbbVie will continue to own the market. Payors could, theoretically, encourage doctors to try cheaper but similarly efficacious and convenient alternatives – *UCB Group*'s *Cimzia* (certolizumab), for example, or *Bristol-Myers Squibb Co.*'s *Orencia* (abatacept) – on *new* patients. But because the new-patient market isn't growing quickly, that's at best a niche business.

And even as a niche business, it only really exists if payors are willing to create it. But they won't. Doing so would violate many of AbbVie's rebate deals on Humira, which by and large forbid plans from preferring any drugs to Humira. And as meager as are the rebate percentages most of our plan clients get from Humira, the total dollars they receive, given Humira's market share, are significant. Without a large market share (impossible to achieve without convincing physicians to switch their stabilized patients), a competitor can't possibly make up the difference between what a plan would lose from forfeiting its AbbVie rebate and what it could get from even a much larger rebate percentage on a drug that's barely used.

The lesson for payors? Don't let new drugs establish Humira-like market dominance.

Second lesson: nip in the bud widespread prescribing of new expensive drugs. Here the object lesson has been *Gilead Sciences Inc.*'s *Sovaldi* (sofosbuvir). As with virtually all drugs that preceded this breakthrough medicine for hepatitis C, it took months for payors to come up with the coverage policies that set the rules for its use and reimbursement.

In the meantime, physicians – understandably – began using the drug for as many of their HCV patients as they could – anyone with the virus, no matter whether they were symptomatic or not. Sovaldi was, after all, the first effective, tolerable cure for this intractable disease.

Once payors did implement restrictions – limiting coverage to people with significant fibrosis, for example – physicians and patients objected, filing coverage reviews, appeals, and exceptions, all of which cost plans plenty.

Some patients went to court – like the woman in Los Angeles suing her insurer, Anthem Blue Cross, for denying coverage on *Harvoni* (sofosbuvir/ledipasvir), Gilead's Sovaldi follow-on, because she's not symptomatic enough. Certainly, such lawsuits will arise with any restrictions – but they'll have a lot more weight if plaintiffs can show that other patients, in the same situation, received the therapy because the same coverage rules weren't in place.

The result: as new medicines are coming to market, payors are preparing in advance at least draft coverage policies (we know because we're involved) so that when these drugs are approved, they'll be able to move quickly to limit their use through strict label-only coverage and plenty of step-edits and prior authorization. Prescribers will simply not be allowed to get used to prescribing one drug until the plans can sign deals that, one way or the other, allow them to limit a drug's economic impact by keeping a lid on pricing or by restricting volume – or, more likely, both.

The Advantage For Payor-Friendly Followers

In short, if the lessons for payors are not to let new drugs establish dominant positions, to deny manufacturers the advantage of incumbency, then the advantages of best-in-class and first-in-class shrink. Indeed, the real financial and practical advantages might go to companies with follow-on drugs who have the luxury of piggybacking on outcomes data developed by earlier-to-market competitors (as did Pfizer in the statin class) or who deliver more payor-relevant data once the class has been established.

Given this background, let us play out what might happen with the most anticipated new class of drugs in recent history – the lipid-lowering PCSK9 inhibitors.

The first two drugs are likely to be released in July and August from the *Regeneron Pharmaceuticals Inc.*/*Sanofi* partnership (alirocumab) and Amgen (evolocumab). The FDA willing, Pfizer will probably release its entry, bococizumab, a year or so later, followed a year or two after

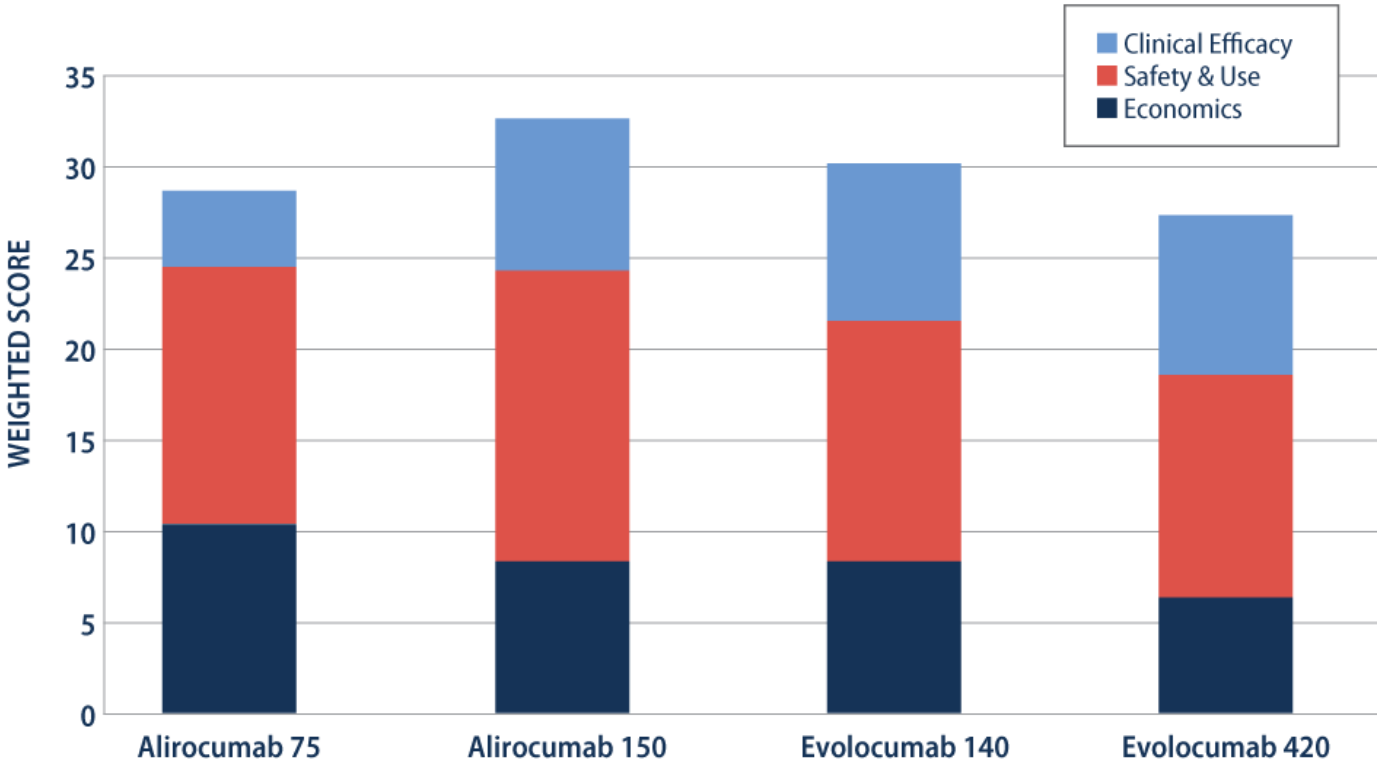
that by *Eli Lilly & Co.*'s LY3015014 and then ALN-PCSsc from a partnership between *Alnylam Pharmaceuticals Inc.* and *The Medicines Co.*

The first point to make is that payors are scared. One of our clients – a large regional plan – is estimating that the PCSK9is will cost it anywhere between $43 million and $300 million, depending, among other things, on the breadth of the label approved.

This plan also believes, based in part on RealEndpoints' *RxScorecard* analysis (*see Exhibit 3*), that the first two PCSK9is could be fundamentally interchangeable – and that it will choose one and exclude the other brand based entirely on the deal it gets. Meanwhile, it will implement strict coverage policies with easiest access limited to the very small fraction of patients with familial hypercholesterolemia (FH). CMS may not allow such restrictiveness for Medicare patients – but this plan, at least, will likely put both its Medicare Advantage and commercial beneficiaries under the same restrictions until CMS tells it to do otherwise.

Exhibit 3

RxScorecard: Nearest-To-Market PCSK9is Are Highly Comparable



RxScorecard is an analysis of the relative value of competitive drugs from the point of view of payors; the higher the score, the more valuable to a payor. Results in the RxScorecard for lipid disorders reflect apples-to-apples comparisons on 10 elements of efficacy, 10 within safety and

use, and five within economics. Because none of these drugs are approved, we used estimated pricing based on analyst estimates and discussions with our payer clients. We assume low-dose alirocumab will be priced significantly lower than the higher dose version. Details of the analysis, which also includes other PCSK9is as well as the CETP inhibitors and Esperion's ETC-1002, are available upon request.

SOURCE: RealEndpoints' *RxScorecard* for Lipid Disorders

In fact, our RxScorecard analysis gives a slight edge to Regeneron/Sanofi's *Praluent* (alirocumab), developed in a more payor-friendly fashion. For example, Regeneron/Sanofi is astutely providing a low-dose formulation that doesn't provide the magnitude of cholesterol-lowering of the high-dose version but does allow conservative doctors to see how patients react to less intensive therapy, presumably at a significantly lower cost.

But for FH patients, alirocumab's advantages can certainly be outweighed by aggressive pricing from Amgen on *Repatha* (evolocumab). And even if Regeneron/Sanofi counters with matching rebates, payors will keep the access door open just a crack until there's cardiovascular outcomes data. Both competitors have outcomes trials ongoing but it's tough to believe that, granted the data are positive, plans won't assume it's a class effect and apply it freely to follow-on PCSK9s, which can simply ride for free on their competitors' investments.

If they're smart, PCSK9i follow-ons will take the money they're saving by not having to do near-term outcomes trials and spend it on payor-focused and differentiating Phase III trials, learning from the mistakes of their predecessors (or at least picking up the opportunities their predecessors let fall in the race to be first). They'll focus on endpoints beyond LDL-C (Regeneron/Sanofi didn't report on *any* endpoints beyond 12 weeks for its low-dose formulation, for example). They'll do a much better job of reporting data by population subsegment, a strategy that has turned out to be an important component of the new HCV competitors' strategies. The blunderbuss initial trials from the early PCSK9i entrants didn't, for example, segment out women. At best they described the patient characteristics at the front end – and then pooled all the data together at the end of the trial.

New players coming with appropriate dosing, data, and pricing – and more or less equivalent efficacy and safety – will be able to take significant share at what we bet is significantly lower total development and marketing cost.

And so a message to biopharma: in a therapeutics world where value is defined both medically and economically, the first player to market – or the player with what will only be temporarily viewed as the best product – won't necessarily be the ultimate winner (particularly if winning is defined as creating a dominant product like Humira). In fact, if he's unlucky, or inflexible, he'll simply have cleared the road for his competitors.

Roger Longman (roger.longman@realendpoints.com) is the CEO of RealEndpoints, an analytics company focused on defining the relative value of drugs for its payor, provider and biopharma clients. He previously founded and co-led Windhover Information, IN VIVO's original publisher.