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Smart Segmentation: Success In The Payer-Dominated Pharma Marketplace

by Roger Longman

As physicians lose decision-making authority to payers, argues Roger Longman of Real Endpoints, drug companies need to segment markets more effectively: the patient populations prescribers are most likely to treat and that will spark the fewest access battles; and the specific payer lines-of-business least inclined to block new drugs' use.

- It’s no secret that physicians are losing decision-making power and payers are gaining it. But even for companies that recognize the shift, understanding what payers want isn’t simple: they are simply too various.
- There is one unifying principle: lacking predictability around a drug’s budget impact, plans are far more likely to exclude a new product, implicitly or explicitly, from their formularies, punishments from which it’s very difficult to ever recover.
- To prevent exclusion, companies must both demonstrate that the drug provides obviously disproportionate value to a well-defined target patient population relative to competitors and credibly define the new drug’s budget impact.
- The bad news: it will be the rare drug whose initial targeted population will meet the most optimistic expectations around total prescription volumes. The good news: targeted strategies work – and, appropriately constructed, deliver outsize investment returns.

Let’s be clear: the fundamental assumption on which the pharmaceutical industry’s commercial model was based and still operates – the primacy of the physician as medical decision-maker – is about as valid as centering news businesses around press runs and print ads.

There are certainly therapeutic islands in this industry where the assumption is temporarily useful (oncology, most obviously, or rare, particularly childhood, diseases). But these are strung out across the vast number of disease categories like Pacific archipelagos yard-by-yard losing

land to rising seas.

Not that physicians don't have prescribing influence. If they don't ask for a drug in the first place, if it doesn't seem important to test out, it won't of course get prescribed. But do individual physicians wield the power of choice within classes, or even to experiment with new drugs unavailable on formularies? Not so much – to not at all.

There seem to be plenty of pharma executives who are ignoring this tectonic shift in industry landscape (either out of ignorance, or willfully, because they've promised the Street they'd hit particular sales targets). And many have paid the price in poor launches.

But it's been almost equally destructive to acknowledge the change – and yet misunderstand it. We note, for example, a series of excellent articles by the editors of *The RPM Report* starting from the premise that "when it comes to prices, the interests of manufacturers are … diametrically opposed to those of consumers and their agents (insurers, public and private)." (*(Also see "Changing The Subject (Part 1): Stop Trying To "Win" The Drug Pricing Debate*" - Pink Sheet, 25 May, 2016.)*and (Also see "Changing the Subject (Part 2): Turning Turing Around By Offering A "National Center Of Pharmaceutical Supply"*" - Pink Sheet, 25 May, 2016.).)

But it's hardly that simple. Employers are certainly worried about the rapid increase in specialty drug cost. Patients worry about their *share* of drug cost, which may or may not have much to do with the price. But neither employers nor patients have much direct influence on specific coverage policies. They've entrusted drug-cost management to agents – insurers, pharmacy benefit managers (PBMs), specialty pharmacies – who can sometimes *make* money on drugs – and the higher priced the better.

The bigger issue for these agents, specifically insurers, is the *predictability* of expense. That's because, by and large, they pass on medical costs to their customers, either directly or through premiums. The primary question for a Medicare plan, for example, is how to accurately bid for new business – pricing premiums high enough to account for the underlying medical and pharmacy costs but not so high that they'll lose business to a plan with sharper forecasting skills. And even the most sophisticated health plans do a pretty poor job of predicting the three key components of a pharmaceutical's economic impact: price, usage and rate of uptake.

Given this unpredictability, not to mention the underlying cost increases that so distress payers' clients, it's generally easier to limit the use of expensive drugs or find cheaper alternatives. That's why payers and PBMs have excluded more and more brand-name drugs from the prescribable pharmacopeia – either explicitly ("we will not pay for this drug") or implicitly, through a whole series of increasingly restrictive barriers. A doctor, or more likely, the office staff, might be able to fill out a 40-question prior authorization form, but they're not likely to do so very often.

For the pharmaceutical company, such exclusions result at best in an extended commercial coma with severe long-term sequelae: it dulls or even kills physician curiosity. If physicians can't experiment with a new drug, at least on some patients, there's little hope that they'll demand its availability later.

That's why the single most important task around drug launches is to make sure that the new drugs aren't excluded. And to prevent exclusion, drug companies must generally do two things. The first is always necessary: demonstrate in a way a payer will credit that the drug provides obviously disproportionate value to the target patient population relative to competitors. The second is usually necessary (and always a good idea): make sure that a payer understands the new drug's budget impact. The drug industry has largely failed to do either.

To define these principles in a bit more detail, we think there are three basic tasks:

1. Objectively assess the value of the drug, from the payer's point of view, relative to existing and coming competition in all relevant subpopulations – and then determine the patient population in which the drug shows disproportionate value.
2. Define the economic impact, in that population, on each line of a payer's business, recognizing that different lines will see different values to a drug (e.g., the commercial fully insured business vs. the Medicare Prescription Drug Plan line).
3. Build a launch strategy around the results: a development program designed to prove the disproportionate value within the target subpopulation; a commercial plan constructed to fit the task (perhaps more spending on hubs, less on sales reps?); and a payer communication strategy, put into action 24 months prior to launch, that credibly defines the likely economic impact on each line of business within the plan and to the plan overall.

The bad news: it will be the rare drug whose initial targeted population will encompass the entire market that its manufacturer's more optimistic commercial executives foresee. And it will take time and patience to expand the population beyond the initial segment.

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The good news: targeted strategies work – and, appropriately constructed, deliver outsize investment returns, even if their topline sales don't fit the blockbuster expectations of executives raised in an era when physicians made the decisions and didn't have to take drug economics into account.

Scaring Payers Into Shutdown Mode

In early 2015, as the market prepared for the likely introduction later in the year of a pair of drugs for dramatically reducing LDL cholesterol ("bad" cholesterol), so-called PCSK9 inhibitors, a flow of stories began to appear about their likely financial impact.

PBMs led the discussion. Along with most payers and their actuarial consultants, they had misjudged the impact of *Gilead Sciences Inc.*'s launch of the hepatitis C medicine *Sovaldi* (sofosbuvir), with payers ending up spending billions on unexpected therapy costs. The warning about the PCSK9 was in part a way to make up for that mistake by *virtually shouting* the possibility that the new drugs could cost US payers $50 billion to $100 billion (which, to put that into context, is one-eighth to a quarter of the total US drug expense). The unspoken but scary implication: the new drugs would replace ubiquitous, cheap statins.

But it was also true that the manufacturers didn't much allay payer fears by more narrowly defining, into readily quantifiable subsegments, the specific patients to be targeted. Yes, the manufacturers did limit the market and communicated that fact to payers, telling them they'd focus on "high risk" patients (more or less: patients with atherosclerotic cardiovascular disease and LDL cholesterol of greater than 100). But for most payers, that definition covers a lot of people – and, to most payers, it's not clear how many. Payers were also worried by the hazy definition around another potential use of the drugs – statin intolerance. What exactly was it? How much of it was real? How would one know? How many people had the condition?

Far more limited, and importantly, easier for payers to define and, to at least some degree, enumerate through ICD-10 codes, would be patients at *very* high risk, those patients for whom a new lipid-lowering therapy would be most logical – patients with multiple serious risk factors (e.g., patients with both heart disease and blockages in peripheral arteries or super-high uncontrolled LDL, or both heart disease and diabetes, or those who'd had a heart attack in the previous 12 months).

Rattled by the PBMs, uncertain about the demographics, payers also didn't have a good idea of the price. One major national plan, for example, met with the manufacturers four to five months before launch and asked, having signed a confidential disclosure agreement (CDA), for some definition around price. One of the manufacturers suggested, according to the head of this payer's pharmacy program, "the higher end of the $7,000 to $9,000 range. And then just a few months later, at launch, we saw the price: $14,000. What message did that send us?"

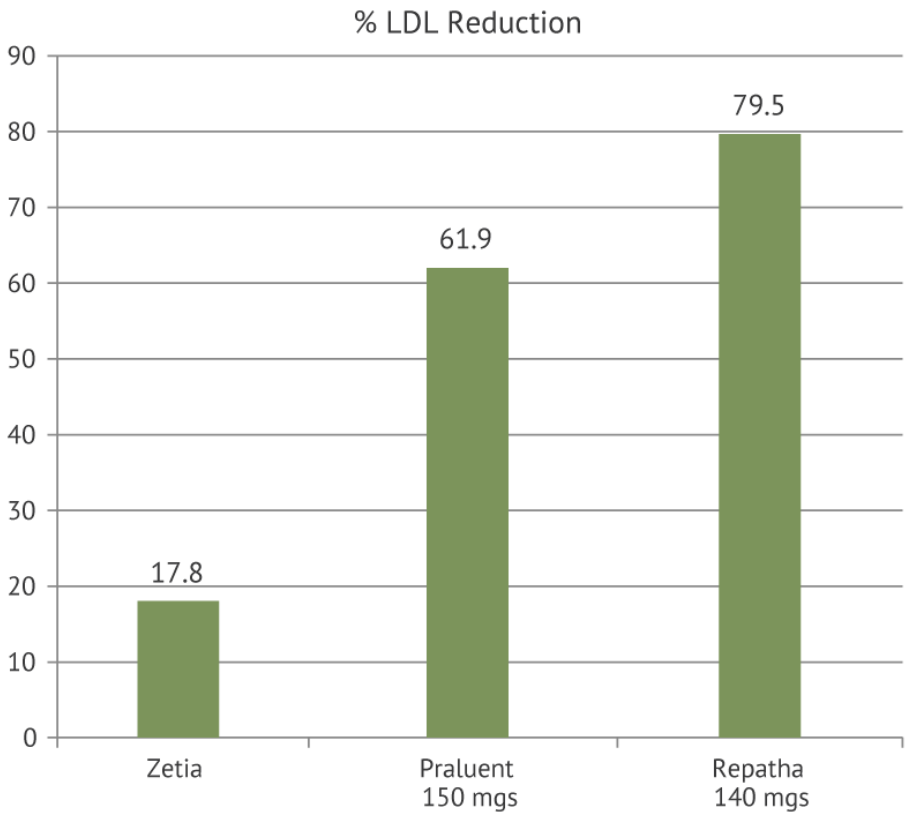
Clueless about the price, this payer was also clueless about uptake. Most payers didn't know how cardiologists, who prescribe mostly oral generics and don't deal with too much payer oversight about their choices, would react to the injectable PCSK9is and their inevitable coverage restrictions. "We projected [for the first few months of 2016] 3,000 PCSK9i scripts," says the pharmacy program head. "In fact, we got 300 – physicians simply didn't write for the drugs." And because this payer was so uncertain about physician reaction and thus impact, its coverage policy, written shortly after launch, basically shut down approvals: in that period, it approved three prescriptions.

On the surface, this doesn't seem so bad for the payer: much lower costs. The problem was the revenue side. Blowing its estimates on the PCSK9s, this plan charged noticeably higher Medicare premiums than other plans and probably lost several thousand beneficiaries to its competition, figures this executive. "Net net, balancing lower revenues and lower costs, we might have come out the same," he says – but lost in terms of building the business with new customers.

Proving Disproportionate Value

Perhaps more importantly, the manufacturers didn't prove, from the payer's point of view, disproportionate value in the broader population segments in which the drugs look like they could be used. The lead story for both *Sanofi*/*Regeneron Pharmaceuticals Inc.*'s *Praluent* (alirocumab) and *Amgen Inc.*'s *Repatha* (evolocumab) was their dramatic reductions in LDL cholesterol versus the leading non-statin, *Merck & Co. Inc.*'s *Zetia* (ezetimibe) – 3.5 times the reduction for Praluent and 4.5 times for Repatha. (*See Exhibit 1*.) But as the payer input into RealEndpoints' *RxScorecard* analysis showed, LDL was worth only about 20% of the total efficacy score; 50% went to outcomes (reduction of total mortality and cardiovascular events and deaths). But at launch, neither PCSK9i could provide outcomes data, whereas Zetia could (it didn't have great data, but at least it had some). So while in the *RxScorecard* payer-focused evaluation the two drugs certainly showed better efficacy than Zetia, they didn't show as much as the LDL benefit would have implied. (*See Exhibit 2*.)

Exhibit 1

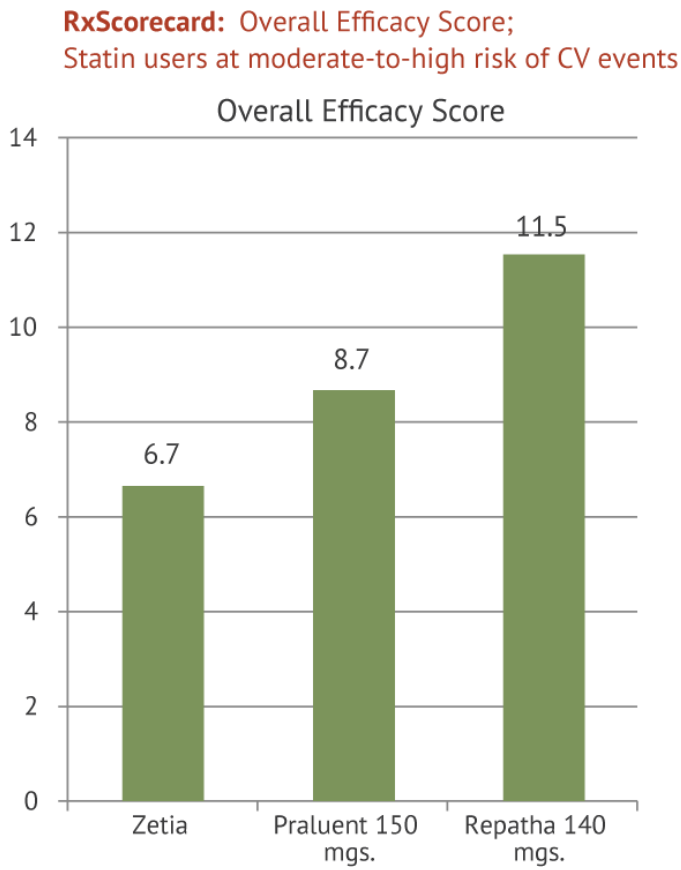


Note: RxScorecard analysis includes results only from IMPROVE-IT, ODYSSEY LONG TERM, and LAPLACE2 trials. Percentages are placebo adjusted. Data from moderate-to-high risk patients with sub-optimal response to statins.

RxScorecard

Exhibit 2

- Looking at overall efficacy (including outcomes), Repatha and Praluent superior to Zetia...but not by the same margin shown in LDL reduction.
- Payers weight outcomes (such as preventing heart attacks and strokes) more heavily than anything else. Praluent and Repatha had no outcomes data at launch – Zetia's very modest outcomes data helped shrink efficacy difference.



Note: RxScorecard analysis of these drugs in moderate-to-high risk patients with sub-optimal response to statins.

RxScorecard

When the analysis turned to safety and ease of use, Zetia won handily. It was a daily oral, not an injectable; it had a long safety history – Zetia, unlike the PCSK9i's, was a known and convenient quantity. (*See Exhibit 3.*) Payers found it easy to require patients to be "stepped through" Zetia before getting a PCSK9i – and there has been no significant backlash from physicians.

It's always easy in hindsight to say what the companies should have done. But it does seem logical to suggest that much tighter patient targeting – say, on very high-risk patients for whom dramatic LDL lowering would have been a prescribing trigger and whose numbers, tightly defined, were less scary to the insurers' actuaries – might have at least got the drugs used more than they have been, giving prescribers a bit more comfort with these new and powerful agents. (*See Exhibit 4.*) Presumably, too, companies' commercial efforts could have been more focused – fewer reps needed, for example – and therefore less expensive.

Payer Centricity

Even those companies that seem to put payers at the center of their strategy often stumble because they don't recognize clearly enough that payers aren't monolithic. Payer preferences, goals and incentives vary plan to plan and, of equal importance, *within* plans, based on each individual line of business. (*See Exhibit 5.*)

Let's start with the latter. For some plans, for example, cost-offsets matter. For others, they're irrelevant – or worse.

The situation is by no means theoretical. *Novartis AG* ran straight into this complication when it launched its heart failure drug, *Entresto* (sacubitril/valsartan).

This remarkable medicine has been proven to reduce cardiovascular events, and thus at least mitigates the cost of cardiovascular disease. The Institute for Clinical and Economic Review (ICER), a US-focused cost-effectiveness watchdog that rarely finds a drug that it believes is appropriately priced, reported that Entresto delivers value for money, more or less at its list price. And Novartis has obligingly offered up outcomes-based reimbursement: if Entresto doesn't reduce cardiovascular events, its effective price drops. (*(Also see "Aetna: Entresto's Label Enabled Outcome-Based Risk Share*" - Scrip, 29 Jun, 2016.).)

What's Not To Like?

The problem is that many — probably most — of the likely Entresto patients are in Medicare and most of those in Medicare Prescription Drug Plans (PDPs). PDPs are responsible for the cost of drugs (Medicare pays roughly two-thirds; the plan must take care of the rest through its premium). But they get no benefit for cost-offsets – because it reduces cardiovascuar events, this is one of Entresto's major economic advantages. Indeed, PDPs don't want heart failure patients, who tend to bring with them lots of co-morbidities and thus higher drug expenditures, reducing profit for these kinds of payers. So making it easy for their beneficiaries to get Entresto only encourages enrollment from the kinds of patients they don't want.

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As for its outcomes-based arrangements: *Cigna Corp.*'s commercial business signed up – but not its Medicare group. Such a deal would merely have increased the likelihood that sicker patients,

with more drug costs, would have joined the Cigna PDP to get access to Entresto. If the drug worked as advertised, the cost to Cigna would stay relatively high. If it didn't, the PDP would still be paying more in drug costs than it was before (Entresto replaces generic ACE inhibitors and ARBs) and it would have sacrificed any spread it makes by buying generics more cheaply than it "sells" them (via reimbursement to Medicare and patient co-pays). (*(Also see "Cigna's Bradbury Talks PCSK9 Contracts And Value Versus Volume*" - Pink Sheet, 11 May, 2016.).)

And as with the PCSK9is, payers were scared about the number of patients – as many as 5 million with heart failure. Defining the target more carefully around high-risk groups would at least have done something to reassure payers. And Novartis might have been more likely to establish a beachhead from which it could later grow the patient base.

Is it therefore any wonder that pharmacy departments at many PDPs are making it hard to prescribe Entresto and, thus, that Novartis has struggled to sell a drug otherwise perfect for this specific patient population?

Launching Successfully Into The New Pharma Marketplace

Companies should be paying close attention to the case studies of the most challenging launches. But they should be paying attention as well to those recent launches that have succeeded – including those that have succeeded without paying much attention at all to payer concerns.

Vertex Pharmaceutical Inc.'s cystic fibrosis follow-on drug *Orkambi* (lumacaftor/ivacaftor), for example, was approved virtually at the same time as the PCSK9is. It's vastly more expensive (roughly $259,000 annually). And even though CF affects a tiny fraction of the number of even very-high risk dislipidemia patients (perhaps 8,500 patients in the US), Orkambi's label is far broader than that of its predecessor drug, *Kalydeco* (ivacaftor).

And with a billion dollars in US sales predicted for 2016, the drug makes a difference to budgets. It works well for some of the patients for whom it's indicated, but not nearly as well for many others.

Exhibit 3

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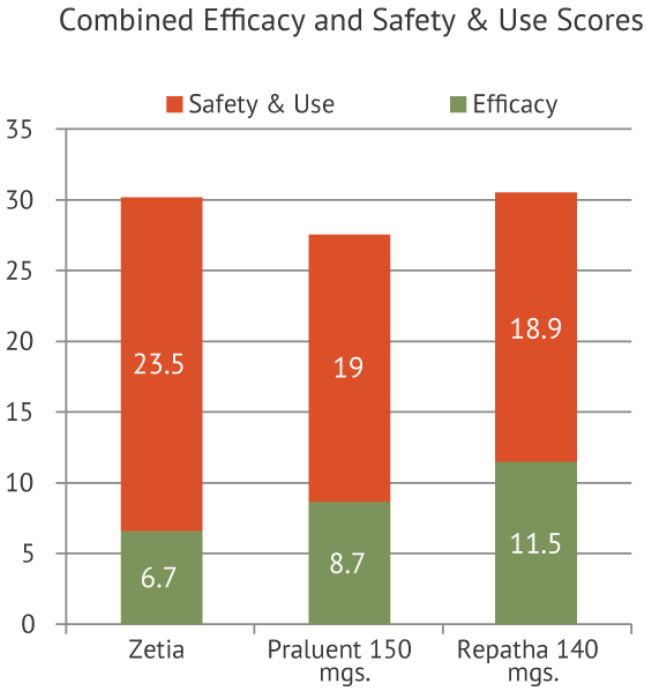
- Zetia has been around longer so it has a well-established safety profile; Praluent and Repatha had only been studied in patients for a limited amount of time and only in clinical trials.
- Payers think that Zetia, a 1x/day oral drug, is more likely to encourage adherence; patients on Praluent and Repatha have to self-inject.

RxScorecard: Overall Safety/Ease of Use Score; Statin users at moderate-to-high-risk of CV events



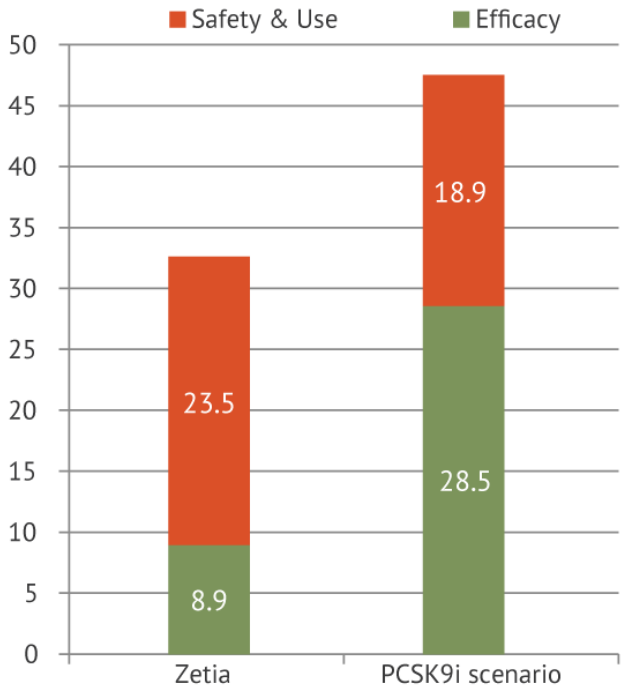
Note: RxScorecard analysis of these drugs in moderate-to-high risk patients with sub-optimal response to statins.

RxScorecard

Exhibit 4

- Patients with atherosclerotic cardiovascular disease, LDL>100 and another serious cardiovascular risk (e.g., recent heart attack).
- Outcomes data less important in this patient population given population is smaller and definable – less concerning to payers...even with a PCSK9i priced at a justified premium to Zetia.

RxScorecard: Combined Efficacy and Safety/Ease of Use; Very high risk statin users



RxScorecard

Theoretically, Orkambi's use can be managed: its studied effects are easily measured and the relatively small number of patients concentrated among specialist prescribers make tracking these metrics fairly simple.

Nonetheless, payers have been virtually unable to limit use. Several of our payer clients have established coverage policies that stop paying for the drug after six months if it doesn't work. But at least two senior plan medical executives have told us that almost certainly they won't cut these patients off: given that the competition to Orkambi is so skimpy, the potential publicity of a CF patient denied coverage to the Vertex drug, even without evidence that it's working, would be too damaging.

Vertex certainly proved that Orkambi delivers disproportionate value relative to the competition – so much value that most restrictions are mere tokenism. But it's also a good example of the relativity of disproportionate value: Orkambi's efficacy is far less for its targeted population than Kalydeco's for its much smaller group. But in a disease that creates such emotional intensity, its superiority over the competition is magnified as is its ability to sidestep payer management.

Winning In A Competitive, Skeptical Marketplace

But even in areas where payers can control the field, drug companies can succeed in opening

access to their products without much compromise on price – granted they both provide disproportionate value and segment the market effectively. Take *Novo Nordisk AS*' obesity drug *Saxenda*,(liraglutide) a higher-dose formulation of its GLP-1 anti-diabetic *Victoza*. Saxenda is roughly five times the cost of its three flailing competitors, Orexigen Therapeutic Inc.'s *Contrave* (naltrexone plus bupropion), Vivus Inc.'s *Qsymia* (phentermine plus topiramate) and Arena Pharmaceutical Inc.'s *Belviq* (lorcaserin).

Exhibit 5

Note: Assumes that each line of business has 20K beneficiaries and same coverage policies; also assumes some medical and drug cost-offsets: replaces $750/beneficiary existing drug spend and reduces ER visits by 2% with average ER cost of $2,000. ASO retains 10% of rebate; PDP plan retains 70%; fully insured plan retains 100%.

Real Endpoints analysis

And payers certainly haven't made things easy for Novo or for any of the newer obesity drugs, which are burdened with significant step edits and prior authorizations when not outright blocked from the formulary. And yet of the Big Four national payers, only United Health advantages any of the three newer, and cheaper, competitors ahead of Saxenda.

One major reason: Novo has de-fanged arguments about Saxenda's high price by focusing, relative to its competitors, on a much more narrowly defined, high-risk group of obese patients treated mostly by endocrinologists and diabetologists, not primary care docs (indeed, when a drug company hires a primary care sales force for a new drug launch, alarm bells go off at payers). In fact, Saxenda's label isn't much more restrictive than Contrave's, Qsymia's or Belviq's – but Novo made it clear to payers that it was targeting a well-defined group of substantially fewer patients.

Another advantage of the strategy: because Saxenda's specialized prescribers know Victoza and the patients well, they're comfortable using the drug, which isn't true for its competitors. In short, if most of these drugs have the same payer restrictions (and despite Saxenda's higher price), physician preferences can tip the scales.

Smart Segmentation For A New Customer Base

Reviewing the challenges many new drugs have faced, we often hear pharmaceutical executives say something to the effect of "payers care only about money – not improving health." And it's certainly true that financial performance drives much payer decision-making.

But complaining about payer incentives does little to advance the strategic conversation. What all these case studies show is the necessity, on the one hand, to objectively measure value of a

new drug from a payer's point of view, and, on the other, define its likely economic impact on the payer as a whole and on each line of its business.

If the drug doesn't deliver clearly defined, disproportional value to the targeted population relative to the competition, payers will set up a damaging access contest of one kind or another. And disproportional value can't be defined by a company's own R&D and marketing executives: they are both too close to the subject and hardly credible to payers. Imagine the FDA's reaction to a company using its own clinicians to test its therapies on patients, all the while knowing which patients were getting drug and which placebo.

There is, in short, no excuse for companies not to stress-test their compounds' relative value in one of the value frameworks on which payers themselves are increasingly relying, such as RealEndpoints' *RxScorecard* or ICER's Evidence Reports (they can use a straw-man version). Indeed, CMS itself is intimating that it might use value frameworks for Part B drugs, and there's every reason to believe they'll expand the notion to Part D.

Part and parcel of understanding value to payers is understanding economic impact: clearly defining and then communicating likely costs to payers, for whom accurate forecasting is a fundamental operating requirement.

But part and parcel of understanding value to payers is understanding economic impact: clearly defining and then communicating likely costs to payers, for whom accurate forecasting is a fundamental operating requirement. And that means a much clearer qualitative and quantitative description of the total population to be treated, an approximate price and an estimate of the rate of uptake. And as Novartis and others have discovered, the calculations need to be run across a payer's entire book of business because each of those lines have different economics. Indeed, a pharma's strategy may in fact start with targeting the specific lines of business at payers for whom the new drug's economic impact is least painful – or even profitable.

Call it smart segmentation: armed with a clear understanding of relative value and targeted population, the drug company can then put together a payer-focused development and commercial strategy: the endpoints required to demonstrate value, the resonant messages and the size and sales resources the project demands.

For drug launches today, the key is to avoid implicit or explicit exclusion; to get the drug into the doctors' hands. Only then will it be possible to build a broader business based, as always, on proof of benefit and a sharp reckoning of what providing that benefit will cost.

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