What Do Pharmaceuticals Really Cost in the Long Run?

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ABSTRACT

OBJECTIVES: To estimate the long-run average cost (LAC) for a typical drug, accounting for the effects of generic competition and medical cost offsets.

STUDY DESIGN: Descriptive analysis of retrospective cross-sectional survey data.

METHODS: We estimated the LAC for a drug as the average price per unit paid over the lifecycle of the drug, discounted across all time periods using Medical Expenditure Panel Survey data, and accounted for the effects of generic competition and medical cost offsets attributable to the use of pharmaceuticals.

RESULTS: The average market-weighted price fell rapidly after generic entry. As a result, the brand price in the year prior to generic market entry was 39% (95% confidence interval [CI], 37%-43%) higher than the LAC per 30-day supply or package. When accounting for medical cost offsets, the brand price in the year prior to generic market entry was 75% (95% CI, 69%-79%) greater than the LAC per 30-day supply or package. The brand price at launch was 11% more than the LAC, and 40% more than the LAC net after adjusting for medical cost offsets.

CONCLUSIONS: Branded drug prices might overstate the true long-run cost of pharmaceuticals by 40% to 75%, accounting for generic price reductions and medical cost offsets. To ensure that all drugs providing long-run value end up entering the marketplace, market access and other policy decisions should consider the full range of long-term costs—and not just prices—at a particular point in time.

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The policy debate over the price of prescription drugs continues to intensify. For example, the recent introduction of very expensive and highly effective treatments for hepatitis C, along with innovative therapies for many cancers, has deepened concern about patients' ability to afford innovative medicines.[1-4] However, the debate does not consider the effect of patent expiration and the loss of exclusivity on drug prices. The price of prescription drugs depends on the nature and consequences of generic competition. Criticism has swirled around a cadre of generic drug manufacturers inflating prices for long-established compounds that, for various reasons, lack generic competitors. For instance, the price of digoxin, an "ancient" treatment for heart failure and atrial fibrillation, deemed an essential medicine by the World Health Organization, doubled over 6 months.[5] However, for many widely used drugs, generic competition reduced prices significantly—and swiftly. Patent expiration lowered the price of simvastatin by 89% in 5 years and the price of clopidogrel by 46% in 1 month.[6,7] These conflicting anecdotes provide little guidance to policy makers about the extent to which patent expiration lowers the long-term cost of drugs. Much has been written about the ability of drugs for specific diseases to reduce the need for other medical costs, yet little is known about the extent these "cost offsets" lower long-term costs associated with the average drug.

To address these knowledge gaps, we estimated the long-term cost of prescription drugs to patients, accounting for patent expiration and medical cost offsets. Focusing on the price of a drug at a given point in time can help inform discussions on which patients should use a drug and what the aggregate costs will be at that point. However, the value of innovation depends on the long-term cost of a new drug, and this has not been quantified previously.

METHODS

Conceptual Framework

Drugs add long-term value to society when each unit sold produces a long-term benefit that exceeds long-term cost. To facilitate the

assessment of long-term value, we estimated the long-run average cost (LAC), defined as the long-run cost per unit of the drug. We derived a formula for the LAC that formalizes this intuition (**eAppendix**, available at **ajmc.com**).

The formula expresses the LAC as an average cost per unit of a drug. To illustrate imagine that a branded drug costs $5 per fill and its generic equivalent costs $1 per fill Imagine further that, over the lifecycle of the drug, 1000 branded prescriptions are filled and 5000 generic prescriptions are filled. The LAC is given by the weighted average cost per fill, which equals: ($5 × 1000 + $1 × 5000) / (1000 + 5000) = $1.40.

TAKEAWAY POINTS

Using Medicare Expenditure Panel Survey data (1996-2013), this study estimated the long-run average cost (LAC) for an average pharmaceutical, accounting for the effects of generic competition and medical cost offsets.

- Focusing on branded drug prices may significantly overstate the LAC.
- Accounting for patent expiration, the loss of exclusivity price and the launch price overstate the LAC by 39% and 11%, respectively, and the LAC net of medical cost offsets by 75% and 40%, respectively.
- To ensure that all drugs providing long-run value end up entering the marketplace, value assessments or related market access decisions should consider these long-term costs.

Apart from generic price reductions, there are 2 additional factors we incorporated into this simple framework. First, a given drug may be produced as multiple dosages or by multiple manufacturers. Thus, the LAC calculates prices and quantities across a number of different dosages and product types. Continuing with the example above, suppose the drug comes in 5-mg and 10-mg doses, and each dosage accounts for half of branded fills; the 5-mg dose costs $2.50 and the 10-mg dose costs $7.50. In this more complex setting, we continued with our principle that the LAC was given by the weighted average cost per fill, which equals: ($2.50 × 500 + $7.50 × 500 + $1 × 5000) / (500 + 500 + 5000) = $1.40.

Second, timing matters. Using a prescription today is worth more than delaying until tomorrow. In economic analysis, this is known as the social discount factor, which measures the rate at which consumer well-being decreases from delaying consumption. Following the economics literature, we employed a 3% annual discount rate.[8] Continuing with the earlier example, suppose that our hypothetical drug was on patent for 1 year only, generics entered after that year, and all drugs sold in year 2 were generic. The discount factor would enter our LAC calculation (in italics) as follows: ($2.50 × 500 + $7.50 × 500 + $1 × 5000 × *[1 – 0.03]*) / (500 + 500 + 5000 × *[1 – 0.03]*) = $1.68. Discounting lowers the contribution of future prescriptions and thus shifts up the LAC in the direction of current period prices. In the eAppendix, we demonstrated proof that the LAC, as formulated here, possessed the following desirable and intuitive property: a drug adds incremental value to society if, and only if, the value per prescription exceeds the LAC.

We next incorporated medical cost offsets in the LAC. We took the average reduction in cost per prescription occurring as a result of avoided nondrug medical costs from the literature. We applied this cost reduction to the LAC to derive the LAC net of medical cost offsets (LAC net). A formal expression for the LAC net can be found in the eAppendix. As an example, we supposed that our hypothetical drug saved 25 cents in medical costs per prescription sold. This cost offset would enter our calculation (in italics) as follows: ([$2.50 – *$0.25*] × 500 + [$7.50 – *$0.25*] × 500 + [$1 – *$0.25*] × 5000 × [1 – 0.03]) / (500 + 500 + 5000 × [1 – 0.03]) = $1.43. Notice that adding the cost offset brought down the LAC by exactly 25 cents. In our empirical analysis, we were particularly interested in how the LAC and the LAC net compared with the price of the drug at the time of generic entry and at launch.

Measuring Market Prices

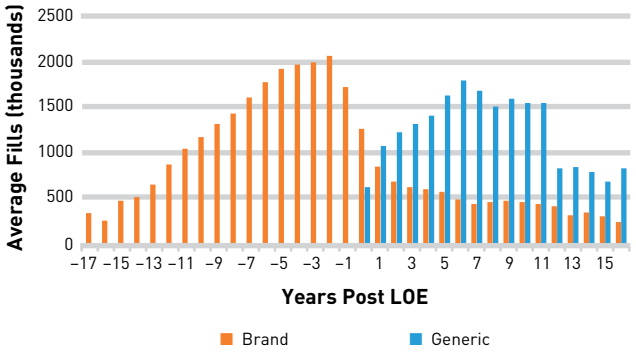
The first step was to estimate prices for a wide sample of drugs. The host database for the price analysis was the Medical Expenditure Panel Survey (MEPS) Prescribed Medicines File from 1996 to 2013.[9] The MEPS data are nationally representative, with detailed information on healthcare use, expenditures, sources of payment, and health insurance coverage. It has a household component that provides respondents' self-reported information, including utilization of prescribed medicines.

We defined the year of loss of exclusivity (LOE) as the first year we observed utilization of a generic National Drug Code (NDC) for a drug. The sample of medicines included those drugs whose LOE occurred in 1997 or later. Within this sample, we observed drug prices as early as 17 years before LOE and up to 16 years after LOE. For example, if a drug lost exclusivity in 2000, we observed prices for 3 years pre-LOE and 14 years post LOE. There were no biologics present in the sample because we did not observe LOE before 2013. We also excluded vaccines, medical devices, prescribed vitamins, and drug classes not meant for immediate patient use.

The MEPS Household Component and pharmacy follow-back surveys measured pharmacy transaction prices. Rebates paid by the manufacturer to the insurer (eg, through the Medicaid Drug Rebate Program or contractual agreements negotiated between manufacturers and private insurers) were excluded. Prior literature has estimated that MEPS aggregate drug spending figures are modestly higher (3%) than national benchmarks,[10] possibly due to the exclusion of rebates and other potential sources of measurement error. We conducted a sensitivity analysis to assess the potential effect of passed-through rebates on our estimates by lowering MEPS branded drug prices by 10% during the exclusivity period.

For each instance of drug utilization in the MEPS, the database records the associated NDC. As a single drug may have multiple NDCs, we used the Medi-Span Electronic Drug File to create a

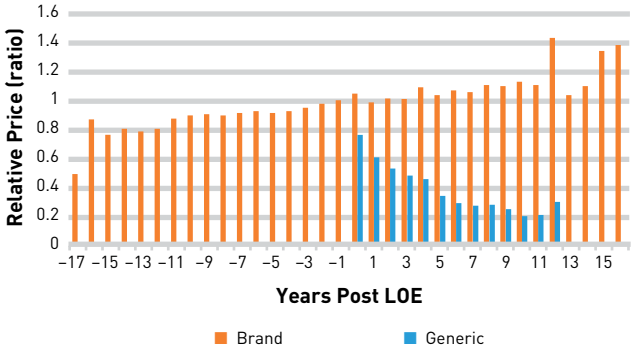
FIGURE 1. Average Brand and Generic Utilization by Year[a]



LOE indicates loss of exclusivity.

[a]From the Medical Expenditure Panel Survey Prescribed Medicines Files, 1996 to 2013.

FIGURE 2. Average Price Relative to Brand Price in the Year Prior to Generic Entry, per Year and 30-Day Supply or Package



LOE indicates loss of exclusivity.

crosswalk from the NDC number to a drug–dose level identifier and linked this crosswalk to the MEPS data by NDC. Medi-Span is a database of drug and clinical information including active ingredients, generic equivalents, and therapeutic class.

Prices were aggregated from the NDC level up to the drug–dose level in 3 stages. First, as each MEPS respondent could have had multiple purchases of the same NDC within a year, we calculated the average price paid per individual by year and NDC. Then, we constructed the national average by computing the survey weighted average price for each NDC by year across users of that NDC. Lastly, we calculated the NDC utilization weighted average of each drug by dose (or package size), type (brand or generic), and year.

Our sample included 132 therapeutic classes, 259 drugs, and 1229 different drug–dose combinations. The sample contained all drugs that experienced LOE during the sample window, with the exception of the exclusions noted above. This covers a broad set of drugs for a wide variety of diseases. We observed prices and utilization of these drugs from 1997 to 2013.

Measuring Quantity

We measured quantity as the number of prescription fills of a drug, dose (or package size), and type (brand or generic) per year. Quantities were aggregated up to the national level by summing the product of the MEPS survey weight and number of fills for each unique individual using a particular drug, dose, and type by year.

Measuring Cost Offsets

Lastly, we estimated the direct medical cost offset per prescription fill. We conducted a targeted literature search for reviews and meta-analyses on the effects of pharmaceutical use on direct costs or medical/nonpharmaceutical spending. The goal was 2-fold: to estimate the direct cost offsets associated with pharmaceutical use and determine a plausible range of effects for medical cost offsets. We searched for estimates of the reduction in direct costs/medical expenditures associated with the use of a wide group of drugs, rather than only a few specific classes, for 1 month (30-day supply).

RESULTS

Pharmaceutical Utilization and Prices Over Time

Figure 1 illustrates that the average number of brand fills declined significantly after LOE (year post LOE of 0) and was more than offset by a concomitant increase in generic users in the following years. In the year generics entered the market, they captured 33% market share on average. This rapid capture of market share is consistent with previous research.[8,11] After 5 and 10 years, generics possessed 74% and 77% of the market, respectively.

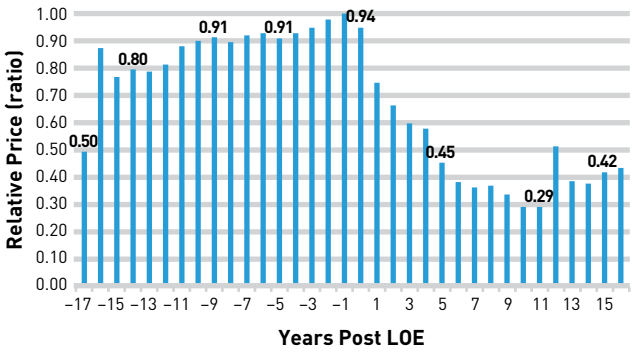
Figure 2 depicts the year-to-year time series for average brand or generic price relative to the price in the year before generic entry (LOE price). The average brand price increased throughout the drug's lifecycle, but the average generic price tended to decrease for at least 10 years. The average generic price was 66% below the LOE price 5 years after generic entry and 80% below 10 years after generic entry.

Figure 3 presents the implications for the price of the average prescription (generic or branded) sold in the marketplace. This Figure demonstrates that the average market-weighted price fell rapidly after generic entry. In the year generics entered the market, the market price was 6% lower than the LOE price. After 5 years, it was 55% lower than the LOE price, and after 10 years, it was 71% lower.

Cost Offsets

Next, we explored the extent to which medical cost offsets reduced the long-term cost of pharmaceuticals. Our targeted literature search generated 13 articles on direct cost offsets associated with pharmaceutical use and/or pharmaceutical spending.[12-22] Four of

FIGURE 3. Market-Weighted Price Relative to Brand Price in the Year Prior to Generic Entry[a]



LOE indicates loss of exclusivity.

[a]Authors' analysis of data from the Medical Expenditure Panel Survey Prescribed Medicines File, 1996 to 2013.

these studies contained information and estimates that allowed for the calculation of the effect of pharmaceutical use on medical (nonpharmacy) spending. Only 1 study, from the Congressional Budget Office (CBO), was representative of a large population (Medicare beneficiaries) and a broad set of therapeutic classes.[22]

In 2012, the CBO estimated that a 1% increase in the number of prescriptions filled per year resulted in a 0.2% (95% confidence interval [CI], 0.1%-0.4%) decrease in medical expenditure per year. Based on the 2012 CBO study[22] and information on the aggregate number of prescription fills and total healthcare expenditures in 2014, we estimated that each additional prescription filled (30-day supply) reduced medical expenditures by $94 per year ($8/month) (**Table 1**).[22-24] The cost savings in Medicare for specific chronic conditions, including diabetes and hypertension, were even higher.[25]

Long-Run Average Cost

We first calculated the LAC, which reflects the effects of generic entry and price declines. We reported this as a fraction of the LOE price and estimated that the LOE price was 39% (95% CI, 37%-43%) higher than the LAC per 30-day supply or package (**Table 2**).

LAC Net of Cost Offsets

We calculated direct medical cost offsets of $94 per year ($8/month) then estimated the LAC net after applying this cost reduction to the drug prices in the data. On average, the LOE price was 75% (95% CI, 69%-79%) greater than the LAC net per 30-day supply or package.

Pharmaceutical Costs Relative to Launch Prices

The analysis above compared the LOE price with LAC and LAC net. Another relevant comparison was to the brand price at launch. This calculation was more difficult, because the length of our sample window did not allow us to follow many drugs from launch well into the post–patent expiration period. As a rough approximation, we calculated the average percentage difference in price between the year prior to generic entry and the average year of launch. Using the FDA Orange Book Data, we found that for the average small molecule, 14 years elapse between the drug launch and the LOE. Moreover, according to Figure 3, the (real) brand price 14 years prior to generic entry was 80% of the price in the year just prior to generic entry. The LOE price was 39% more than the LAC and, thus, it follows that the launch price was 11% (= 1 – [0.8 × 139%]) more than the LAC. Similarly, the launch price is 40% (= 1 – [0.8 × 175%]) more than LAC net.

DISCUSSION

As it is well understood that generic entry lowers prices, policy makers should consider the long-term cost of pharmaceuticals, rather than the cost at a particular point in time. We showed that these price reductions meaningfully lowered the average cost per prescription that patients pay over a drug's lifetime. Branded drug prices were 11% above the LAC at launch and 39% above the LAC at patent expiration. Incorporating cost offsets brought these differentials to 40% and 75%, respectively, above the LAC net. Noting that long-run generic prices lie 80% below the branded price at patent expiration, the LAC net was roughly halfway between the pre-expiration branded price and the long-run generic price.

Branded prices, generic prices, and the LAC all play important roles in economic decisions, which are made on the margin. Prices at a point in time matter to payers, who must decide if the benefit of treating 1 more patient outweighs the cost. The LAC and the LAC net, however, should matter to regulators, policy makers, and payers assessing whether a new drug can be marketed or reimbursed. In this context, overstating the eventual cost of a drug may lead to fewer drugs being made available, weaker incentives to innovate, and ultimately, fewer new drugs discovered. The use of the LAC and the LAC net could mitigate these effects by informing decision

TABLE 1. Calculation of Direct Cost Offset Parameter

Percent Change in Direct Costs for a 1% Increase in Number of Prescriptions Filled	Change in Number of Prescriptions Filled ($, billions)[a]	Medical Expenditures ($, billions)[a]	Direct Cost Offsets Per Year	Direct Cost Offsets Per Month
a	b	c	d = a × (c / b)	e = d / 12
−0.2	4.003	$1889.70	−$94	−$8

[a]From 2013 to 2014, patients in the United States filled 4 billion prescriptions and spent $1889.7 billion on medical care.[22-24]

TABLE 2. LAC and LAC Net of Cost Offsets in Relation to Branded Prices 1 Year Prior to Generic Entry[a]

Measure	Point Estimate	95% CI
LOE price as a percentage of LAC	139%	137%-143%
LOE price as a percentage of LAC net	175%	169%-179%

CI indicates confidence interval; LAC, long-run average cost; LAC net, long-run average cost net of medical cost offsets; LOE, loss of exclusivity.
[a]Authors' calculations using 1996 to 2013 Medical Expenditure Panel Survey data.

makers about the true value drugs add to society along all their lifecycle. For example, health technology assessments (HTAs) could include an assessment of the cost-effectiveness ratio that discounts the launch price—the most frequently used measure of drug cost—by 11% (excluding cost offsets) or 40% (including cost offsets). Not only should HTAs incorporate medical cost offsets, but they should also consider the long-run unit cost of a drug.

As research has demonstrated, robust generic drug markets play a key role in holding down the LAC of drugs. Thus, policy makers should aim to mitigate barriers to entry for new generic drugs and ensure the continued safety of the generic drug supply. This is particularly relevant for specialized products that do not attract significant generic entry or competition. Recent events (eg, the 5000% overnight price increase of daraprim) demonstrate the importance of preserving competition within those market segments.[26]

Medical cost offsets play a material role in holding down the LAC. This suggests the importance of taking an integrated view across pharmacy and medical benefits. Some have argued that standalone prescription drug insurers offer less-efficient benefit designs because they fail to internalize spillovers between prescription drugs and medical care.[27]

Limitations

Our estimate of the LAC may have overstated the actual LAC because we lacked data on rebates paid from manufacturers to payers. These may have been significant during the period of patent protection. Our analysis was also limited by the timeframe of the MEPS data. We were only able to characterize trends in price and utilization for drugs that lost exclusivity in 1997 or later; thus, we could only observe the first 15 years after LOE, even though many drugs were used for more than 15 years following LOE. On the other hand, we observed up to 16 years prior to LOE, likely covering the vast majority of the patent-protected period when market prices are highest. Therefore, our estimate might overstate the LAC.

Our estimate covered only the population of drugs for which generics end up being used. Although this is not fully representative, this represented the vast majority of drug utilization. In 2013, for instance, drugs with generic alternatives represented at least 86.4% of prescription drug utilization in MEPS and these generic alternatives presented 81.0% of prescription drug utilization in MEPS. As some of the remaining 13.6% will inevitably include some patent-protected drugs that will eventually go generic, this is a conservative estimate of the fraction of use due to drugs with generic utilization.

Another limitation concerns the estimate of direct cost offsets. Our estimate is based on a CBO study of medical cost offsets over a broad sample of drugs for Medicare beneficiaries.[22] It is possible that cost offsets within Medicare may be different from the effects in the non-Medicare population. Future research might consider estimating cost offsets outside Medicare in a broad-based sample for comparison. We also took a conservative approach to measuring the cost offset effects of drugs. For example, the results of several studies suggest that pharmaceuticals produce financial benefits for employers by increasing the productivity of workers with chronic illnesses. Biologics for rheumatoid arthritis, antihistamines for allergies, selective serotonin reuptake inhibitors for depression, and triptans for migraine are commonly studied treatments that have been shown to increase productivity.[28-39] However, as productivity estimates are highly specific to particular classes of drugs, we excluded them from our analysis and our estimate of the LAC net. Future research might explore drug class or disease state–specific LAC and LAC net values that reflect direct and indirect cost offsets.

Finally, our analysis accounted for the LOE of small molecule prices but not biologic prices. Biosimilars entered the US market very recently—the first biosimilar was approved for use in the United States by the FDA in March 2015—and we did not observe their effects on biologic prices in the data. There are lessons to be learned from experiences with biosimilars in European countries, where biosimilar prices are typically about 25% less than the reference biologic (brand) price. The share of the market captured by the biosimilar varies considerably across countries depending on incentives and reimbursement policies.[40-42] Based on the experiences of Germany and Sweden, the countries with markets most comparable to those in the United States, biosimilars could capture a significant share, albeit most likely at a smaller discount than a generic small molecule.

CONCLUSIONS

Branded drug prices might overstate the true long-run cost of brand name drugs by 40% to 75%, accounting for generic price reductions and medical cost offsets. Ultimately, the LAC net lies about halfway between the branded price at patent expiration and the long-run generic price. This point may acquire particular salience for policy makers and HTA bodies measuring the costs and benefits of making new drugs available. HTA reports inevitably rely on a number of modeled outcomes, including utilization, effectiveness, and other key parameters. These reports might also consider building in models of long-run costs that align with the LAC. A simple approach would be for payers interested in a societal perspective to incorporate at least an 11% discount to the brand price at launch to

account for the lower long-run prices of drugs to patients. Focusing only on current brand prices may overestimate the true costs to patients and thus underestimate the long-run cost-effectiveness of new treatments. To ensure that all drugs providing long-run value enter the marketplace, market access and other policy decisions should consider these long-term costs. ■

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eAppendix

The "long-run average cost" (LAC) and the "long-run average cost net of cost offsets" (LACnet) concepts can be formulated mathematically as follows. Define a "drug" as a dosage or formulation sold by a particular manufacturer. Further, define t as the number of periods after the molecule's loss of exclusivity. Define p_{jt} as the real transaction cost of buying drug j, t periods from the loss of exclusivity date. Define N_{jt} as the quantity (fills or users) of drug j utilized in period t.

Before we define the LAC, we begin by defining the average market price of the molecule sold in period t. We compute this by observing all prices paid for the molecule in period t and calculating the market-share weighted average of all these prices, as in

$$P_t \equiv \left\{ \sum_j \frac{N_{jt}}{\sum_j N_{jt}} \frac{p_{jt}}{p_{j0}} \right\}.$$

This expression gives us the average price at a point in time. We calculate LAC as the weighted average of these market prices P_t, weighted according to how much of the drug was used in each period, and appropriately discounted. Define the one-year discount factor as β, in the sense that consumption delayed by one year is worth $\beta < 1$ as much as consumption enjoyed today. LAC is then given by:

$$LAC = \sum_t \sum_j p_{jt} \frac{\beta^t N_{jt}}{\sum_j \sum_t \beta^t N_{jt}}$$

We assume that the social discount factor is equal to the real rate of interest. Essentially, this assumes that society discounts consumption at the same rate that it discounts money overall. The long-run real interest rate has been estimated at 3%, so we use ($\beta = 1 - 0.03 = 0.97$) as our one-year discount factor.

We next incorporated medical cost offsets to our analysis. Defining c_{jt} as the costoffset associated with drug j in period t. Even though it would be desirable to estimate this term for every point in the drug's lifecycle, the variation in cos -offsets over time is not reliably estimated in the existing literature. Therefore, we make the simplifying assumption that medical cost offsets are constant in absolute value. We focus on estimating the average value of medical costs

saved per prescription filled. Defining this cost offset parameter as *c*, the LAC-net for the molecule is then defined as:

$$LAC_{\text{net}} = \sum_t \left[\sum_j (p_{jt} - c) \frac{\beta^t N_{jt}}{\sum_j \sum_t \beta^t N_{jt}} \right].$$

Notice that cost offsets were treated equivalently to price reductions in the sense that a permanent one dollar increase in the price has the same effects as a one dollar cost offset. Also, the LAC (or LAC-net) is intimately connected to the long-term value of a new molecule. In particular, if LAC for a particular drug *j* exceeds the value per unit of that drug, the drug then generates positive value to patients, and vice-versa. Defining v_j as the monetized value of each unit of drug, *j* yields the following equations*:*

The consumer surplus associated with the use of drug *j* is equal to:

$$CS_j = \sum_t \beta^t v_j N_{jt} - \sum_t \beta^t p_{jt} N_{jt}$$

Observe that $CS_j > 0$ if and only if:

$$v_j > \frac{\sum_t \beta^t p_{jt} N_{jt}}{\sum_t \beta^t N_{jt}} = \sum_t p_{jt} \frac{\beta^t N_{jt}}{\sum_t \beta^t N_{jt}} \equiv LAC_j$$

Thus, whether or not patients benefit from drug *j* depends not on the price at launch, but rather on a measure of the lifetime price of that drug, known as LAC_j. Finally, note one useful feature of the lifetime price —it is insensitive to how we normalize the measurement of time. That is, the point at which we begin discounting has no effect.[8]