The Value of Pharmaceutical Product Line Extensions

An Analysis of Medicaid Pharmaceutical Reimbursements 2007-2014

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I. SUMMARY

This paper looks at the financial impact of pharmaceutical product line extensions. In order to do this, I looked at two different relationships: the relationship between product line extensions and the effective life of a drug product line, and the relationship between product line extensions and the change in sales for a product line after generic launch. For this second analysis, I use Medicaid reimbursements as a proxy for US sales.

It is my hope that an improved understanding of these relationships will help investors better value pharmaceutical product lines, assist executives in determining product level strategy, and contribute to the ongoing debate surrounding pharmaceutical life-cycle management.

There is a lot at stake in understanding these relationships. For a drug product line with one billion dollars in annual US sales, every week for which generic entry is postponed produces an additional roughly $17 million in sales. (This calculation assumes the product line would maintain long-term sales after generic entry into the market at 10% of current sales.) For this same drug product line, a one percentage point increase in long-term sales as a percentage of current sales is $10 million in annual sales.

Out of all of the product line extensions I examined, the only one with a significant positive relationship to the change in Medicaid reimbursements after generic entry was new routes of administration. A new route of administration was associated with a 16 percentage point higher level of reimbursements for its associated product line one year after generic entry as compared to a pre-entry baseline. Two years after generic entry, a new route of administration was associated with an 11 percentage point higher level of reimbursements as compared to a pre-entry baseline. By the third year after generic entry, this relationship is no longer statistically

significant. For a billion-dollar drug product line, this translates into roughly $270 million in increased annual sales over two years.

None of the product line extensions had a significant relationship with the effective life of drug product lines. I suspect that the variation in this variable is driven by patents, patent lawyers, and politicians.

II. BACKGROUND

Pharmaceutical companies have a number of strategies that they use to extend the financial life of drug product lines. Some are based on the creation of product line extensions: new formulations, metabolites, single enantiomer drugs, and drug combinations.[1] There are also extension strategies that do not involve products, such as finding a new use for existing drug products and using litigation to prevent generic products from launching in the US market.

Critics of these strategies refer to them as "evergreening," claiming that the economic value added to the company far outweighs the therapeutic value to patients.[2] For instance, a New York Times article from 2013 outlines how Purdue Pharma extended the life of its blockbuster drug, Oxycontin, by developing a formulation that made the product tamper-resistant and harder to abuse.[3] Many, like Techdirt's Glyn Moody, questioned the timing: "I suspect we may see more of these interesting coincidences as other profitable drug patents are about to expire, and their manufacturers start to come up with yet more ways to 'evergreen' them."[4]

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[1] Gupta et al. (2015)
[2] Collier (2013)
[3] Meier (2013)
[4] Moody (2013)

Those who defend these strategies point to the additional value product line extensions bring to patients. Some extended-release versions of drugs, such as Prozac Weekly, show better adherence in clinical studies.[5] Similarly, Nexium, the S-Enantiomer of Prilosec, "achieves significantly greater acid control than omeprazole."[6] While these benefits may not exist for all extensions, they are real and measurable for some.

This paper focuses exclusively on the financial impact of these product line extensions on Medicaid reimbursements, a proxy for US sales. While some of the information in this analysis may inform certain aspects of the evergreening debate, I will avoid all ethical, legal, and clinical questions for now. Prior to any kind of debate about extending the life of a drug product line is the question of whether the strategies being employed to do so even work.

III. METHODOLOGY

I looked at two different relationships to evaluate the financial impact of pharmaceutical product line extensions: the relationship between product line extensions and the effective life of a drug product line, and the relationship between product line extensions and the change in sales after generic launch. To do this, I selected a set of drug product lines to analyze, categorized associated product line extensions and assigned them to their respective drug product lines, determined how to define the effective life of a drug product line, and chose a sales data set to use for the analysis. The rest of this section details these steps. An analysis of the data begins in section 4.

III.1 DRUG SET

[5] Nussbaumer et al. (2014)
[6] Lind et al. (2000)

To develop the drug set, I started with the top 100 drugs in 2006 by US sales. These drugs accounted for roughly 70% of US drug sales that year.[7] I then replaced the drugs that were extensions of a different drug product line with the original New Molecular Entity (NME). For example, I replaced Effexor XR, the #7 drug by US sales, with Effexor. I then eliminated all drugs where a generic entered the market prior to 2007 or after 2014. This left the following 41 drugs. (For a list of the other 59 drugs along with explanations as to why they were excluded, see **exhibit 1**).

LIPITOR	TOPAMAX	ALTACE	CELLCEPT
PREVACID	FOSAMAX	PROVIGIL	KEPPRA
SINGULAIR	ZYRTEC	LIDODERM	SKELAXIN
PLAVIX	COREG	COZAAR	NIASPAN
NORVASC	ACIPHEX	LAMISIL	PROGRAF
SEROQUEL	CYMBALTA	LOVENOX	ARIMIDEX
PROTONIX	CONCERTA	DETROL	XALATAN
AMBIEN	IMITREX	GEODON	AVAPRO
ACTOS	ARICEPT	RHINOCORT	
RISPERDAL	FLOMAX	TRILEPTAL	
ZYPREXA	OMNICEF	YASMIN	

III.2 DRUG PRODUCT LINES AND CATEGORIZING PRODUCT-LINE EXTENSIONS

For the purposes of this analysis, there are two different types of drug product lines. The first type consists of a new molecular entity (NME) and any new dosage forms, enantiomers, or metabolites sponsored by the company or subsidiaries that sponsored the original NME. The second drug product line is a new dosage form, enantiomer, or metabolite sponsored by a different company than the one that sponsored the original NME, along with any additional new dosage forms, enantiomers, or metabolites developed by this second company. New combinations containing the NME are also included so long as a different company sponsored

[7] Drugs.com(2015)

the other compound(s) or a generic form(s) was launched prior to a generic launch of the original NME.

Let me illustrate this with a couple examples. Takeda Pharmaceuticals' Prevacid product line consists of Prevacid (the original NME), Prevacid IV (a new route of administration), Dexilant (the R-enantiomer or Prevacid), Naprapac (a combination of Prevacid with Naproxen, which was sponsored by Bayer) and two additional new dosage forms. Pfizer's Lipitor product line consists of Lipitor (the original NME) and Caduet (a combination of Lipitor and Norvasc, another Pfizer drug whose generic launched four years prior to Lipitor). For a full detailing of product lines used in this analysis, see **exhibit 2**.

I separated product line extensions into six categories: single-enantiomer drugs (ENAN), metabolite drugs (META), extended/controlled/sustained-release drugs (XR), new routes of administration (NRA), all other new dosage forms (NDF), and new combinations (NC). I identified single enantiomer product line extensions by prefix (lev/levo/ar/es/dex/dextro) using the American Medical Association's rules for coining names.[8] I identified metabolite product line extensions using R. Scott Obach's "Pharmacologically Active Drug Metabolites: Impact on Drug Discovery and Pharmacotherapy."[9] I identified all new dosage forms and new combinations using the Drugs@FDA database. I determined drug sponsors using the Drugs@FDA database as well.

III.3 EFFECTIVE LIFE OF A DRUG

To avoid dealing with patent law, this analysis defines the effective life of a drug product line (LIFE) as the number of quarters between the first approval date for the original NME as listed in the Drugs@FDA database and the date of the first generic launch for any product in the

[8] American Medical Association (2015)
[9] Obach (2013)

line. First generic launch is defined as the first quarter with Medicaid US generic reimbursements greater than 1% of total reimbursements for the drug product line. Exceptions to this methodology are Plavix and Rhinocort, where a generic was launched and later pulled from the market. For both of these drug product lines, the generic re-launch date is used in this analysis.

III.4 Sales Data Set

I used the total reimbursements from the Medicaid National Summary State Drug Reports as a proxy for US sales data. It is the only publicly available source of drug sales data broken down by product in the US. Company press releases often include sales by product, but not to the level of detail or in the quantity needed to do this analysis. I would encourage anyone who has access to proprietary quarterly sales data on a product level to redo this analysis replacing my reimbursement data with actual US sales numbers.

To quantify the change in reimbursements, I used the quarter prior to first generic launch as the reimbursement level prior to generic entry. I then looked at reimbursements for the quarter one year (1YRPOST), two years (2YRPOST), and three years (3YRPOST) after this quarter as a percentage of this level. By using the same quarter of the year for all three data points, I hope to account for any seasonal effects in the data. Seasonal effects are pronounced for certain drugs, like Zithromax, an antibiotic with significantly higher Medicaid reimbursements in Q1 and Q4 than in Q2 and Q3.

IV. SURVEY OF THE DATA

Before trying to understand the relationships between the different predictor variables, it is helpful to get a sense of how the individual predictor variables relate to the target variables. To begin, here is a summary of the data gathered using the process in section 3:

Variable	Total Count	Mean	StDev	Minimum	Median	Maximum	Sum
LIFE	41	57.41	23.28	31.00	58.00	191.00	
1YRPOST	41	0.3391	0.2217	0.0257	0.3189	0.9931	
2YRPOST	41	0.2239	0.2048	0.0094	0.1903	1.0132	
3YRPOST	41	0.1919	0.1554	0.0034	0.1440	0.4852	
NC	41						13.0000
ENAN	41						3.0000
META	41						1.0000
XR	41						7.0000
NRA	41						14.0000
NDF	41						28.000

A few summary statistics to note before analyzing the relationships between variables:

- The average LIFE of a drug product line is 57 quarters. This is just over the maximum length of 14 years for Hatch-Waxman patent extension determinations.[10] The longest drug product line LIFE is Skelaxin with an extremely long pre-generic life of 191 quarters, which is over 47 years.
- 1YRPOST generic entry, the drug product line with the lowest reimbursements as a percentage of pre-generic reimbursements is Plavix at 2.6% of its level one year prior. The drug product line with the highest percentage is Rhinocort, whose reimbursements remained nearly unchanged. The average across all drugs is 33%. 2YRPOST generic entry, this percentage drops to 22%
- 3YRPOST generic entry, the average reimbursements as a percentage of pre-generic reimbursements has dropped slightly to 19%. The Lovenox product line has been able to maintain reimbursements at 49% of the pre-generic reimbursements three years post-generic.
- There are 66 total product line extensions (NC + ENAN + META + XR + NRA + NDF) across the 41 drug product lines in the data set.

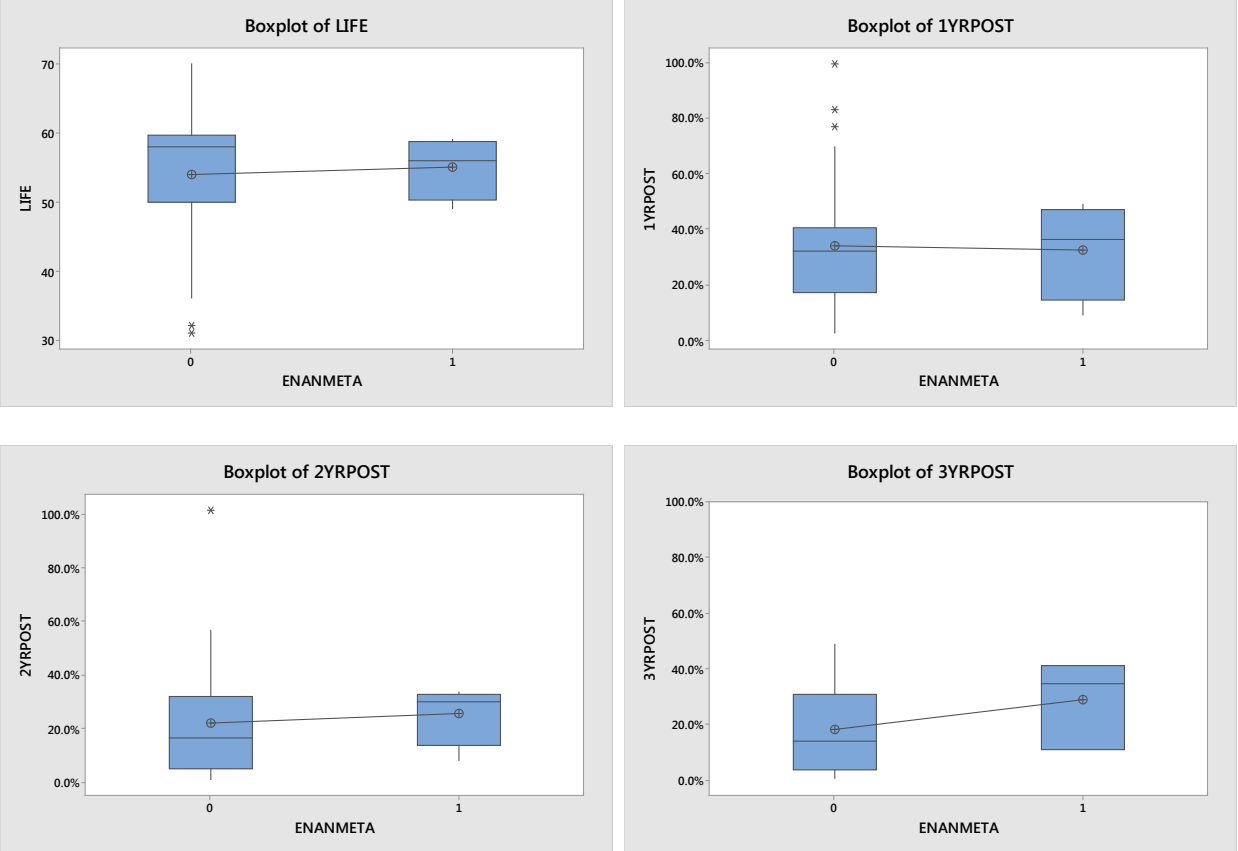
[10] Strongin (2002)

In the rest of section 4, I look at single variable relationships between the employed strategies and the two target variables, LIFE and 1YRPOST. In section 5, I run a regression to account for the fact that predictor variables may interact with each other.

IV.1 ENANTIOMERS AND METABOLITES

In the data, there are three single enantiomer drugs, Dexilant, Xyzal, and Nuvigil, and one metabolite drug, Invega. I will refer to product lines that include these extensions as ENANMETA product lines.

Figure 1. *Boxplots of LIFE, 1YRPOST, 2YRPOST, and 3YRPOST for ENANMETA (1) vs non-ENANMETA (0) product lines*



The sample mean for LIFE of ENANMETA product lines is 1.03 quarters greater than the mean for the rest of the sample. With such a small sample size, a difference this small is not statistically significant with a two-sample t-test P-value of .725.

The sample mean for reimbursements 1YRPOST for ENANMETA product lines is actually lower than the rest of the sample, but by 3YRPOST the mean is 11 percentage points higher. Still, with such a small sample size (p-value of .388), there are no meaningful relationships.

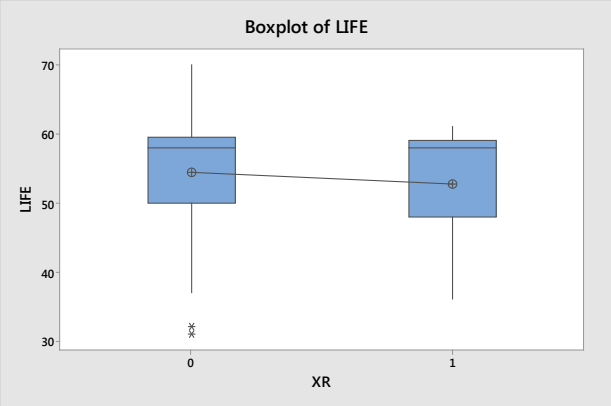
Note that there is wide variability in how the four ENANMETA product lines performed 1YRPOST, 2YRPOST, and 3YRPOST. The Risperdal product line, with its metabolite drug extension Invega, maintained reimbursements at 42%, 33%, and 41% of base year reimbursements. On the other hand, Zyrtec, with its enantiomer extension Xyzal, only maintained reimbursements at 9%, 8%, and 11% respectively. This is likely a result of the FDA's approval of Zyrtec OTC in 2007, just prior to generic entry in the first quarter of 2008.[11]

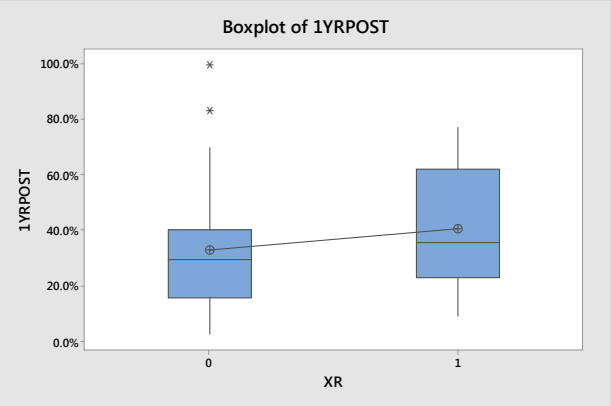
IV.2 Extended-release

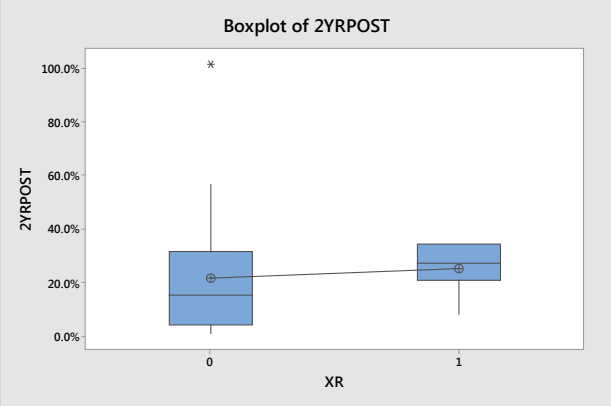
There are seven drug product lines that added some variety of extended-release dosage form (XR) after initial approval: Seroquel, Ambien, Zyprexa, Zyrtec, Coreg, Detrol, and Keppra. Similar to drug product lines with ENANMETA drugs, product lines with XR extensions show a wide variability in their LIFE and reimbursements 1YRPOST, 2YRPOST, and 3YRPOST.

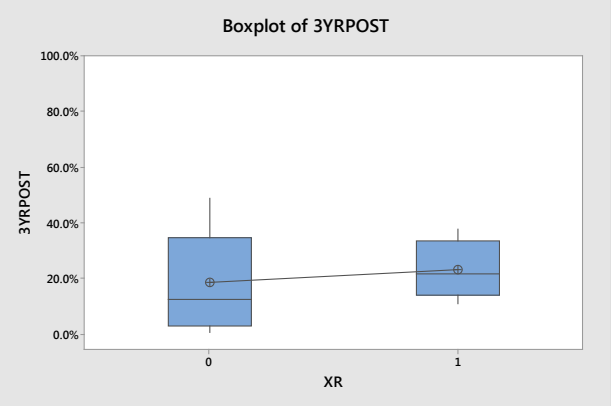
Figure 2. *Boxplots of LIFE, 1YRPOST, 2YRPOST, and 3YRPOST for XR (1) vs non-XR (0) drug product lines*

[11] FDA.gov (2015)









The sample mean for the LIFE of product lines that include XR extensions is 1.65 quarters less than the mean for the rest of the sample. This is far less than the standard deviation based on the sample size.

The sample mean for reimbursements 1YRPOST, 2YRPOST, and 3YRPOST for product lines that include XR extensions is 8, 4, and 5 percentage points higher respectively. Again, none of these values approaches statistical significance.

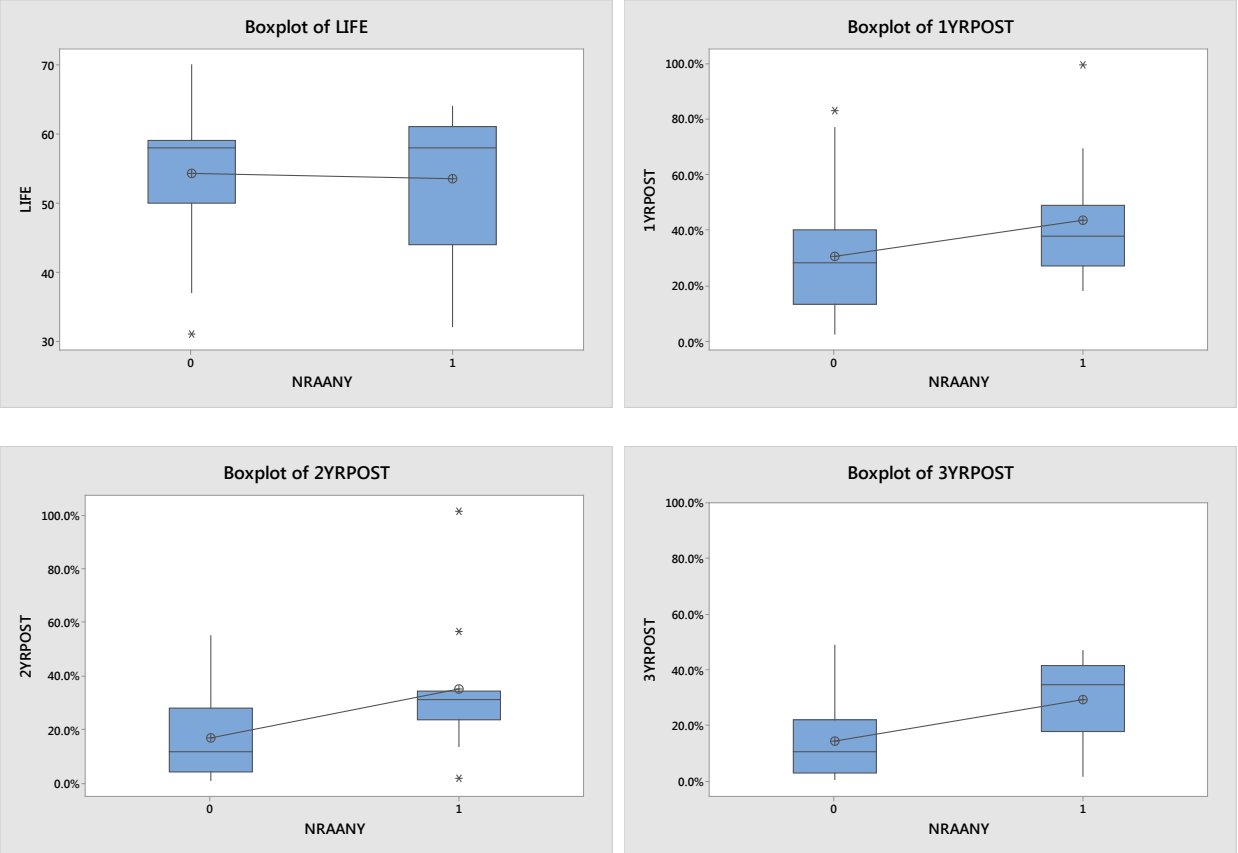
Ambien (62%), Coreg (43%), and Detrol (77%) maintained the highest level of reimbursements 1YRPOST. Keppra (34%) and Seroquel (34%) were the highest 2YRPOST. Zyprexa (23% and 24%) and Zyrtec (9% and 8%) were the lowest both 1YRPOST and 2YRPOST.

This is surprising, as I would expect to see a significant positive relationship. Ambien is a sleep aid and a controlled release version would presumably have some therapeutic benefit. Similarly, Coreg is a beta-blocker used to reduce the risk of death after a heart attack. Perhaps even a slight improvement in adherence could save lives. For Detrol, a treatment for overactive bladder, patients are more likely to adhere to a regimented schedule since they have to take the pill less often. Again, Zyrtec is somewhat complicated due to the launch of an over-the-counter version.

IV.3 New Routes of Administration

Examining drug product lines with new routes of administration (NRA), we begin to see some statistically significant relationships emerge. In total, there are 14 NRAs across 11 different drug product lines. Again, we compare LIFE, 1YRPOST, 2YRPOST, and 3YRPOST for drugs product lines that include NRAs with those that do not.

Figure 3. *Boxplots of LIFE, 1YRPOST, 2YRPOST, and 3YRPOST for NRA (1) vs non-NRA (0) drug product lines*



The mean reimbursements for drug product lines that include an NRA are 13 percentage points higher 1YRPOST with a two-sided t-test p-value of 0.126. The relationship is even stronger 2YRPOST, with a p-value of 0.046. 2YRPOST, mean reimbursements are 18 percentage points higher for drug product lines that include an NRA. This relationship persists 3YRPOST with average reimbursements 15 percentage points higher with a two-sided t-test p-value of 0.025.

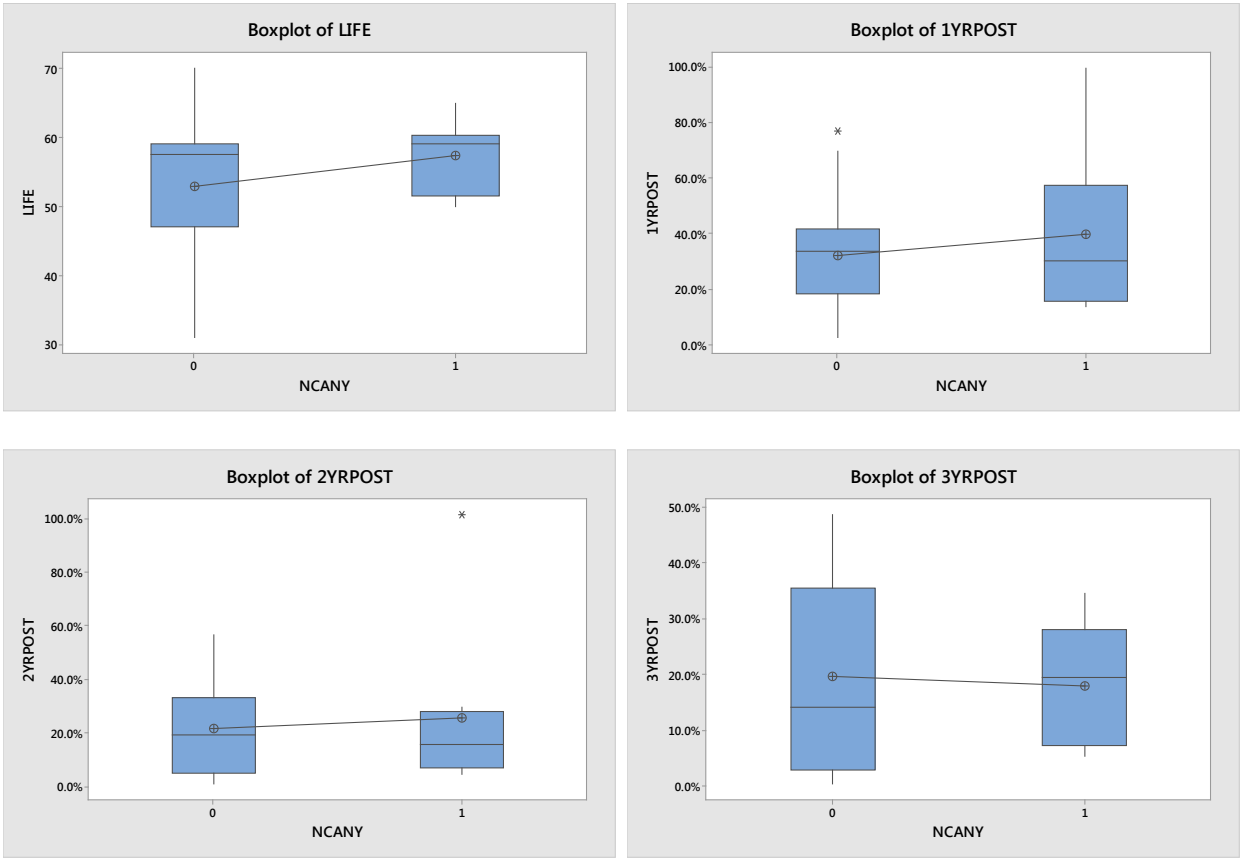
It appears that NRAs have a statistically significant relationship with drug reimbursement levels after generic entry. However, a multivariate regression is required to draw any meaningful conclusions about how these variables are associated with each other.

IV.4 NEW COMBINATIONS AND NEW DOSAGE FORMS

The presence of new combinations (NC) has a moderately positive relationship with the life of a drug product line with a p-value of .08. This is likely a false positive as there is no legal mechanism by which a new combination would help extend the life of a patent. The relationships between NC and 1YRPOST, 2YRPOST, and 3YRPOST are all insignificant.

In contrast, the presence of new dosage forms (NDF) excluding XR and NRA extensions has a moderate negative relationship with the life of a drug product line with a p-value of .06

Figure 4. *Boxplots of LIFE, 1YRPOST, 2YRPOST, and 3YRPOST for NC (1) vs non-NC (0) drug product lines*



V. REGRESSION ANALYSIS

In light of these single variable relationships, I will run a linear regression, using NC, ENANMETA, XR, NRA, and NDF as predictor variables.

V.1 Relationship between predictors and LIFE

As there is a regulatory mechanism for maintaining marketing exclusivity through the use of these extensions, we would expect a relationship between these extensions and the life of a drug product line. Here is the output from a regression of NC, ENANMETA, XR, NRA, and NDF on LIFE (excluding Skelaxin due to its inordinately long LIFE):

Regression Analysis: LIFE versus NC, ENANMETA, XR, NRA, NDF

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	5	182.83	36.57	0.39	0.853
NC	1	70.22	70.22	0.75	0.394
ENANMETA	1	19.14	19.14	0.20	0.655
XR	1	11.56	11.56	0.12	0.728
NRA	1	29.86	29.86	0.32	0.577
NDF	1	58.83	58.83	0.63	0.435
Error	34	3199.95	94.12		
Lack-of-Fit	14	1387.23	99.09	1.09	0.418
Pure Error	20	1812.72	90.64		
Total	39	3382.77			

Model Summary

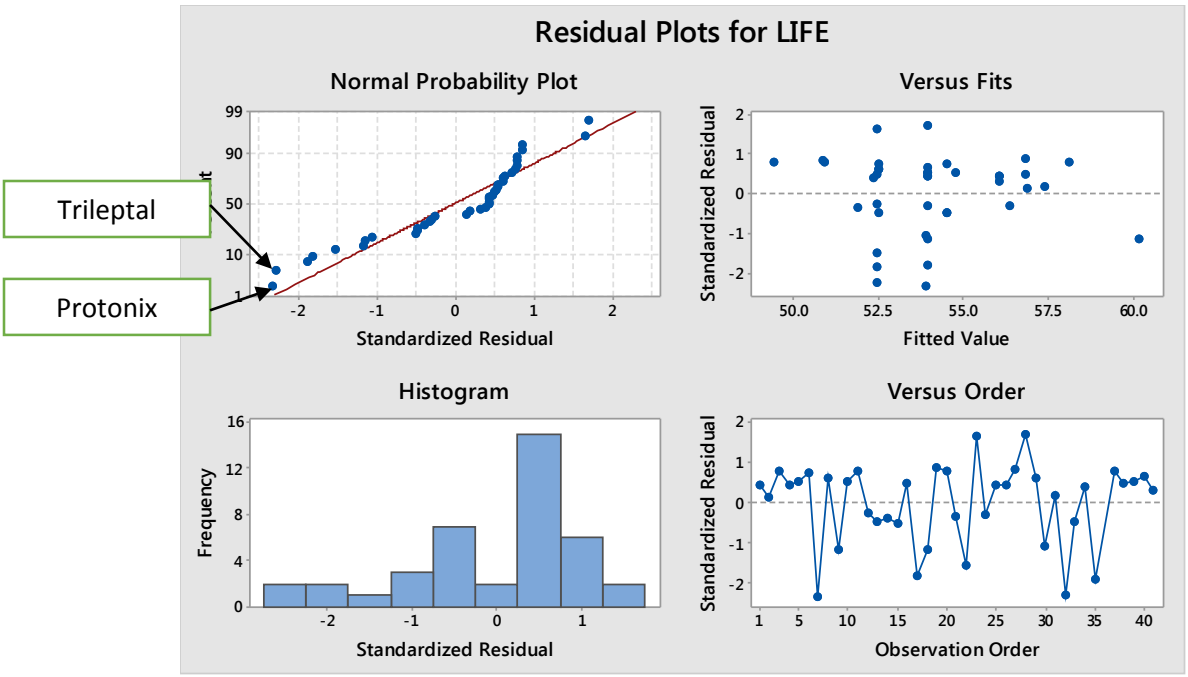
S	R-sq	R-sq(adj)	R-sq(pred)
9.70134	5.40%	0.00%	0.00%

Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	53.96	2.46	21.97	0.000	
NC	2.09	2.42	0.86	0.394	1.04
ENANMETA	2.43	5.39	0.45	0.655	1.11
XR	-1.44	4.11	-0.35	0.728	1.03
NRA	1.45	2.58	0.56	0.577	1.06
NDF	-1.52	1.92	-0.79	0.435	1.20

Regression Equation

LIFE = 53.96 + 2.09 NC + 2.43 ENANMETA - 1.44 XR + 1.45 NRA - 1.52 NDF



There are two outliers, Trileptal and Protonix. The generic for Protonix was launched at-risk – the courts were still deciding the validity of the associated patent.[12] The reason for Trileptal's short life is less clear. Looking at the residual plots versus fits and the histogram of residuals, there appears to be non-constant variance and the residuals appear to be skewed right.

Removing these outliers and re-running the regression leaves us with a similar output. There is no apparent linear relationship between these five predictor variables and the LIFE of a drug product line. There may be something else (I suspect litigation) that drives LIFE.

V.2 RELATIONSHIP BETWEEN PREDICTORS AND 1YRPOST

If product line extensions add real value to a drug product line, we would expect to see higher reimbursements 1YRPOST, 2YRPOST, and 3YRPOST for drug product lines that incorporate these strategies. Here is the output from a regression of NC, ENANMETA, XR, NRA, and NDF on 1YRPOST.

[12] Staton (2013)

Regression Analysis: 1YRPOST versus NC, ENANMETA, XR, NRA, NDF

```
Analysis of Variance

Source         DF   Adj SS    Adj MS  F-Value  P-Value
Regression      5  0.36940  0.073879     1.62    0.181
  NC            1  0.00197  0.001972     0.04    0.837
  ENANMETA      1  0.00105  0.001054     0.02    0.880
  XR            1  0.04206  0.042063     0.92    0.344
  NRA           1  0.32876  0.328761     7.20    0.011
  NDF           1  0.02927  0.029269     0.64    0.429
Error          35  1.59725  0.045636
  Lack-of-Fit  14  0.80568  0.057549     1.53    0.185
  Pure Error   21  0.79157  0.037694
Total          40  1.96665

Model Summary
       S    R-sq  R-sq(adj)  R-sq(pred)
0.213625  18.78%      7.18%       0.00%


Coefficients
Term         Coef  SE Coef  T-Value  P-Value   VIF
Constant   0.2938   0.0524     5.60    0.000
NC         0.0110   0.0529     0.21    0.837  1.03
ENANMETA   -0.018    0.119    -0.15    0.880  1.12
XR         0.0864   0.0900     0.96    0.344  1.03
NRA        0.1519   0.0566     2.68    0.011  1.07
NDF       -0.0337   0.0421    -0.80    0.429  1.20

Regression Equation
1YRPOST = 0.2938 + 0.0110 NC - 0.018 ENANMETA + 0.0864 XR + 0.1519 NRA - 0.0337 NDF
```

At a first glance, we appear to be over-fitting the model with a t-statistic for NRA that is lower than the overall F-statistic for the regression. Looking at a best subsets regression, we see that the variables that maximize adjusted R-sq are NRA and XR. For simplicity, I will run a regression using only NRA.

Best Subsets Regression: 1YRPOST versus NC, ENANMETA, XR, NRA, NDF

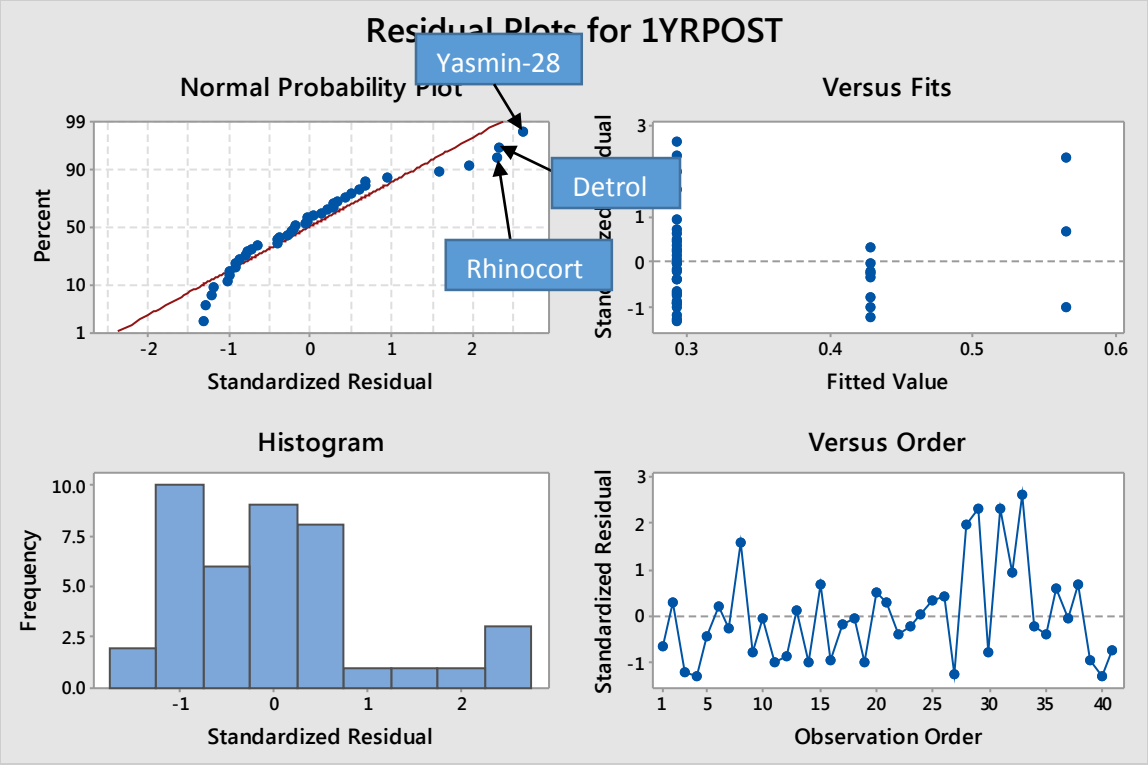
```
Response is 1YRPOST

                                                E
                                                N
                                                A
                                                N
                                                M
                                                E   N N
            R-Sq    R-Sq  Mallows           N T X R D
Vars  R-Sq  (adj)  (pred)       Cp        S  C A R A F
   1  14.4   12.2     2.2     -0.1  0.20772        X
   1   1.8    0.0     0.0      5.3  0.22256      X
   2  16.7   12.3     0.0      0.9  0.20769      X X
   2  16.6   12.2     0.0      0.9  0.20773        X X
   3  18.6   12.0     0.0      2.1  0.20796      X X X
```

```
   3  17.1   10.3     0.0      2.7  0.20996    X X X
   4  18.7    9.7     0.0      4.0  0.21071  X   X X X
   4  18.7    9.6     0.0      4.0  0.21077    X X X X
   5  18.8    7.2     0.0      6.0  0.21363  X X X X X
```

Regression Analysis: 1YRPOST versus NRA

```
Analysis of Variance

Source         DF  Adj SS   Adj MS  F-Value  P-Value
Regression      1  0.2839  0.28386     6.58    0.014
  NRA           1  0.2839  0.28386     6.58    0.014
Error          39  1.6828  0.04315
  Lack-of-Fit   1  0.1164  0.11636     2.82    0.101
  Pure Error   38  1.5664  0.04122
Total          40  1.9666

Model Summary
       S    R-sq  R-sq(adj)  R-sq(pred)
0.207722  14.43%     12.24%       2.22%

Coefficients
Term        Coef  SE Coef  T-Value  P-Value   VIF
Constant  0.2925   0.0372     7.87    0.000
NRA       0.1366   0.0532     2.56    0.014  1.00

Regression Equation
1YRPOST = 0.2925 + 0.1366 NRA
```

Looking at a regression output of 1YRPOST versus NRA, we see a positive relationship between the number of NRAs (albeit, most drug product lines only have one NRA, if any) and the reimbursement level 1YRPOST.



There are three significant outliers, Rhinocort, Detrol, and Yasmin-28. They also happen to be the three drug product lines that maintained sales best after initial generic launch. Yasmin-28's apparent success is most likely the result of bad press prior to the launch of a generic form. The birth control pill is associated with a higher rate of blood clots than other forms of birth control.[13] Since sales were already significantly down by the time a generic entered the market, generic sales made up a larger percentage of Yasmin-28 sales even though sales for both were low. Detrol's apparent success is an artifact of using Medicaid reimbursement data as a proxy for sales. Reimbursements in the Medicaid data tripled in 2013, but Pfizer reported a 21% decrease in US sales for the drug over the same period.[14]

The Rhinocort product line is more interesting. The decreases in reimbursements for Rhinocort and Pulmicort were made up for by a new combination drug, Symbicort. This shows

[13] Voyer (2013)
[14] Pfizer Third Quarter Results (2013)

how one extremely successful product line extension can have a significant impact on the data. This is similar to the success seen with the S-enantiomer Nexium, a drug whose sales are significantly higher than sales of its original NME, Prilosec.

Here is the output if we remove Detrol and Yasmin-28 from the regression and re-run the analysis:

Regression Analysis: 1YRPOST versus NRA

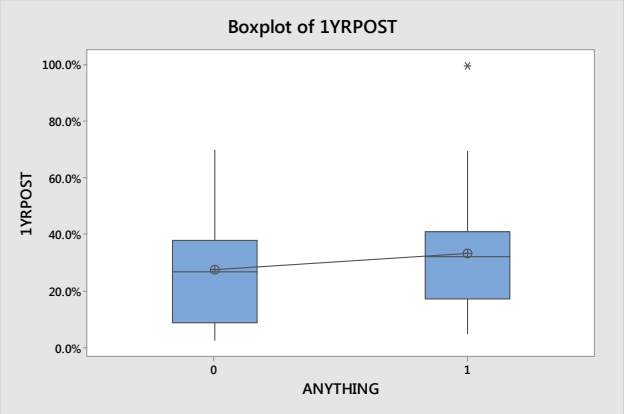
```
Analysis of Variance

Source         DF   Adj SS   Adj MS  F-Value  P-Value
Regression      1  0.38725  0.38725    12.63    0.001
  NRA           1  0.38725  0.38725    12.63    0.001
Error          37  1.13440  0.03066
  Lack-of-Fit   1  0.09171  0.09171     3.17    0.084
  Pure Error   36  1.04269  0.02896
Total          38  1.52165


Model Summary

       S    R-sq  R-sq(adj)  R-sq(pred)
0.175098  25.45%     23.43%      12.19%


Coefficients
Term        Coef  SE Coef  T-Value  P-Value   VIF
Constant  0.2579   0.0324     7.96    0.000
NRA       0.1608   0.0452     3.55    0.001  1.00

Regression Equation
1YRPOST = 0.2579 + 0.1608 NRA
```

Rhinocort is still an outlier, along with Lovenox. The standardized residuals, leverage values, and Cook's distances are low enough that I will leave them in the model. The R-sq for the model is 25.45%, which means the regression accounts for one quarter of the variability in the data. Three-quarters of the variability is left unexplained. Based on our best subsets regression, other product line extensions do not help explain this. I suspect that much of this variability is explained by legal outcomes and marketing. Perhaps these relationships depend on the necessity of the drug to the patient or the prevalence of the underlying condition. All of these subjects could benefit from further analysis.

Based on the standard error of the NRA coefficient, our 95% confidence interval for the true slope of the NRA coefficient is 7 to 25. This is a wide range, but significantly different from 0.

V.3 RELATIONSHIP BETWEEN ANY STRATEGY AND 1YRPOST

There is one more thing to consider. Perhaps there is a relationship between doing any product line extensions (ANYTHING) and 1YRPOST. For this analysis, I coded every drug product line either 1 or 0, depending on whether any product line extensions were launched. Here is a boxplot and the result of a 2-sample t-test.



Two-Sample T-Test and CI: 1YRPOST, ANYTHING

```
Two-sample T for 1YRPOST

ANYTHING   N   Mean  StDev  SE Mean
0         10  0.273  0.202    0.064
1         29  0.330  0.201    0.037

Difference = μ (0) - μ (1)
Estimate for difference:  -0.0577
95% CI for difference:  (-0.2151, 0.0997)
T-Test of difference = 0 (vs ≠): T-Value = -0.78  P-Value = 0.447  DF = 15
```

The relationship between doing ANYTHING and 1YRPOST is not statistically significant, with a p-value of 0.477.

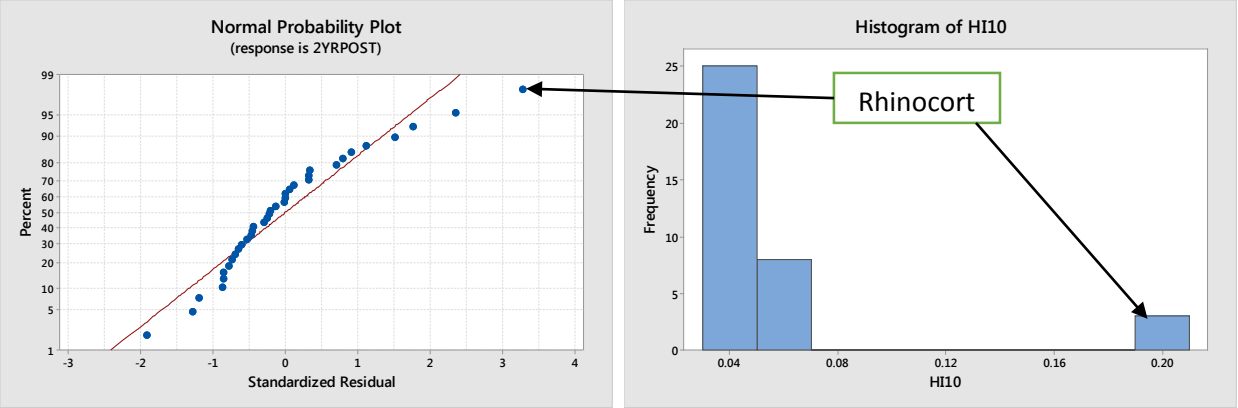
V.4 PERSISTENCE IN THE RELATIONSHIP BETWEEN NRA AND SALES POST GENERIC ENTRY

Does this apparent relationship one year after a generic entered the market persist into later periods? I removed data points where the generic entered the market in 2013 as they have no 2YRPOST data yet. Here is the output from a regression of NRA versus 2YRPOST:

Regression Analysis: 2YRPOST versus NRA

```
Analysis of Variance

Source         DF  Adj SS   Adj MS  F-Value  P-Value
Regression      1  0.4746  0.47462    16.24    0.000
  NRA           1  0.4746  0.47462    16.24    0.000
Error          34  0.9936  0.02922
  Lack-of-Fit   1  0.1082  0.10819     4.03    0.053
  Pure Error   33  0.8854  0.02683
Total          35  1.4682

Model Summary
       S    R-sq  R-sq(adj)  R-sq(pred)
0.170945  32.33%     30.34%      16.52%

Coefficients
Term        Coef  SE Coef  T-Value  P-Value   VIF
Constant  0.1537   0.0334     4.60    0.000
NRA       0.1806   0.0448     4.03    0.000  1.00

Regression Equation
2YRPOST = 0.1537 + 0.1806 NRA
```

The adjusted R-sq jumps to 32%. This appears promising. However, the standardized residual and leverage values for Rhinocort may be giving its values undue influence over the regression. You can see this in the normal plot of the residuals and the histogram of leverages below:



While Rhinocort may be a case study in how to use product-line extensions to successfully extend the financial life of a drug product line, it is probably obscuring the actual relationship between the variables. Here is the output with Rhinocort removed:

Regression Analysis: 2YRPOST versus NRA

```
Analysis of Variance

Source          DF   Adj SS   Adj MS  F-Value  P-Value
Regression       1  0.14669  0.14669     7.11    0.012
  NRA            1  0.14669  0.14669     7.11    0.012
Error           33  0.68071  0.02063
  Lack-of-Fit    1  0.01313  0.01313     0.63    0.433
  Pure Error    32  0.66757  0.02086
Total           34  0.82739

Model Summary
       S    R-sq  R-sq(adj)  R-sq(pred)
0.143623  17.73%     15.24%       7.02%


Coefficients
Term        Coef  SE Coef  T-Value  P-Value   VIF
Constant  0.1633   0.0282     5.80    0.000
NRA       0.1111   0.0417     2.67    0.012  1.00

Regression Equation

2YRPOST = 0.1633 + 0.1111 NRA
```

The adjusted R-sq drops down to 15.24%, which reflects the leverage Rhinocort had in the previous regression. Still, there seems to be persistent value in product line extensions that involve new routes of administration,

Based on the standard error of the NRA coefficient, our 95% confidence interval for the true slope of the NRA coefficient is 10 to 12.

VI. CONCLUSION

The data is much murkier than the debate over evergreening would lead us to believe. There appears to be no meaningful relationship between any of the predictor variables and the life of drug product lines before generics enter the market. The only product line extension with a strong association to reimbursements after generic entry is new routes of administration. The other product line extensions are a mixed bag. Some extensions, like Nexium, appear to be unmitigated successes. Others, like Xyzal, appear to be failures.

To extend this analysis, I would like to add additional drug product lines and find a way to incorporate actual US sales data, marketing spend by product, and patents and other litigation. I suspect these variables account for much of the variation in the data and could help us better understand these complicated relationships.

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Exhibit 1. Excluded drugs

Drug	Reason for Exclusion
Nexium	S-Enantiomer of **Prilosec** (Generic launched prior to 2007)
Advair Diskus	No generic
Effexor XR	Extended Release Version of **Effexor** (Generic launched prior to 2007)
Zocor	Generic launched prior to 2007
Lexapro (Celexa)	S-Enantiomer of **Celexa** (Generic launched prior to 2007)
Zoloft	Generic launched prior to 2007
Wellbutrin XL	Extended release version of **Wellbutrin** (generic launched prior to 2007)
Avandia	No generic
Toprol-XL	XR Version of **Lopressor** (Novartis product) Generic launched prior to 2007
Vytorin	No generic
Abilify	No generic
Levaquin	S-Enantiomer of **Floxin** (Generic launched prior to 2007)
Lamictal	Generic launched prior to 2007
Celebrex	No generic
Lotrel	Combination of **Norvasc** and **Lotensin** (Generic launched prior to 2007)
Valtrex	Prodrug of **Zovirax** (generic launched prior to 2007)
Zetia	No generic
Adderall XR	Extended Release version of **Adderall (**generic launched in 2002)
Enbrel	No generic
Crestor	No generic
Lantus	No generic
Diovan	Generic launched in 2014 due to issues with Ranbaxy manufacturing plant
Tricor	Generic launched prior to 2007
Diovan HCT	Combination of **Diovan** and **Hydrochlorothiazide;** included above
Nasonex	No generic
Viagra	No generic
Actonel	Generic launched in 2014
OxyContin	Generic has been on and off the market; currently no generic
Lyrica	No generic
Zofran	Generic launched first quarter 2007
Spiriva	No generic
Lunesta	Generic launched in 2014
Synthroid	Generic launched prior to 2007
Strattera	No generic
Premarin Tabs	No generic; Teva synthetic form and branded under **Cenestin**
Pravachol	Generic launched prior to 2007
Truvada	No generic
Ambien CR	Included w/ **Ambien** above
Actiq	New dosage form of **Sublimaze** (generic launched prior to 2007)
Depakote	New dosage form of Depakene (generic **Depakene** approved prior to 2007)
Combivent	Combination of **Atrovent** and **Proventil**
Humalog	No Generic
Mobic	Generic launched prior to 2007
Evista	Generic launched in 2014
Humira	No generic
Depakote ER	Included w/ **Depakote** above
Flovent HFA	New dosage form of **Flovent** (generic launched prior to 2007)
Hyzaar	Included w/ Cozaar above
Procrit	No generic
Zelnorm	No generic
Asacol	No generic to oral **Mesalamine** (Asacol)
Namenda	No generic
Cialis	No generic
Reyataz	No generic
Ortho Tri-Cyclen Lo	New dosage form of a combination of ETHINYL ESTRADIOL; NORGESTIMATE
Byetta	No generic
Duragesic	New dosage form of **Sublimaze** (generic launched prior to 2007)
Combivir	Combination of Retrovir and Epivir
Kaletra	No generic

Exhibit 2. Drug product lines

Original Drug	Extensions				
LIPITOR-NME	CADUET-NC				
PREVACID-NME	DEXILANT-ENAN	PREVACID IV-NRA	PREVACID NAPRAPAC-NC	PREVACID ORAL DISINT-NDF	PREVACID SUSPENSION-NDF
SINGULAIR-NME	SINGULAIR CHEWABLE-NDF	SINGULAIR GRANULE-NDF			
PLAVIX-NME					
NORVASC-NME					
SEROQUEL-NME					
SEROQUEL-XR					
PROTONIX-NME	PROTONIX IV-NRA	PROTONIX SUSPENSION-NDF			
AMBIEN-NME	AMBIEN -XR				
ACTOS-NME	DUETACT-NC	ACTOPLUS MET-NC	ACTOPLUS MET XR-NC		
RISPERDAL-NME	RISPERDAL SOLUTION-NDF	RISPERDAL ORAL DISINT-NDF	RISPERDAL CONSTA-NRA	INVEGA-META	
ZYPREXA-NME	ZYPREXA ZYDIS-NDF	ZYPREXA INJECTABLE-NRA	ZYPREXA RELPREVV-XR	SYMBYAX-NC	
TOPAMAX-NME	TOPAMAX SPRINKLE-NDF				
FOSAMAX-NME	FOSAMAX PLUS D-NC	FOSAMAX SOLUTION-NDF			
ZYRTEC-NME	ZYRTEC SYRUP-NDF	ZYRTEC-D 12 HOUR-XR	CHILDREN'S ZYRTEC-NDF	XYZAL-ENAN	
COREG-NME	COREG-XR				
ACIPHEX-NME	ACIPHEX-NDF				
CYMBALTA-NME					
DIOVAN-NME	DIOVAN HCT-NC	DIOVAN TABLET-NDF	EXFORGE-NC	EXFORGE HCT-NC	
CONCERTA-NME					
IMITREX-NME	IMITREX TABLET-NRA	IMITREX SPRAY-NRA			
ARICEPT-NME	ARICEPT SOLUTION-NDF	ARICEPT ORAL DISINT TABLET	ARICEPT TABLET-NDF		
FLOMAX-NME					
OMNICEF-NME	OMNICEF SUSPENSION-NDF				
ALTACE-NME	ALTACE TABLET-NDF				
PROVIGIL-NME	NUVIGIL-ENAN				
LIDODERM-NDF					
COZAAR-NME	HYZAAR-NC				
LAMISIL-NME	LAMISIL TABLET-NRA	LAMISIL SOLUTION-NDF	LAMISIL GEL-NDF	LAMISIL GRANULE-NDF	
LOVENOX-NME					
DETROL-NME	DETROL-XR				
GEODON-NME	GEODON INJECTABLE-NRA	GEODON SUSPENSION-NDF			
RHINOCORT-NME	PULMICORT-NRA	PULMICORT RESPULES-NDF	ENTOCORT EC-NRA	SYMBICORT-NC	
TRILEPTAL-NME	TRILEPTAL SUSPENSION-NDF				
YASMIN-NME	BEYAZ-NC	YAZ-NDF			
CELLCEPT-NME	CELLCEPT TABLET-NDF	CELLCEPT INJECTION-NRA	CELLCEPT SUSPENSION-NDF		
KEPPRA-NME	KEPPRA SOLUTION-NDF	KEPPRA INJECTABLE-NRA	KEPPRA -XR		
SKELAXIN-NME					
NIASPAN-NDF	ADVICOR-NC	SIMCOR-NC			
PROGRAF-NME	PROGRAF INJECTABLE-NRA	PROTOPIC-NRA			
ARIMIDEX-NME					
XALATAN-NME					
AVAPRO-NME	AVALIDE-NC				