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THE REGULATION OF PRESCRIPTION DRUG COMPETITION AND MARKET RESPONSES:
PATTERNS IN PRICES AND SALES FOLLOWING LOSS OF EXCLUSIVITY

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The Regulation of Prescription Drug Competition and Market Responses: Patterns in Prices and Sales Following Loss of Exclusivity
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ABSTRACT

We examine six molecules facing initial loss of US exclusivity (LOE, from patent expiration or challenges) between June 2009 and May 2013 that were among the 50 most prescribed molecules in May 2013. We examine prices per day of therapy (from the perspective of average revenue received by retail pharmacy per day of therapy) and utilization separately for four payer types (cash, Medicare Part D, Medicaid, and other third party payer – TPP) and age under vs. 65 and older. We find that quantity substitutions away from the brand are much larger proportionately and more rapid than average price reductions during the first six months following initial LOE. Brands continue to raise prices after generics enter. Expansion of total molecule sales (brand plus generic) following LOE is an increasingly common phenomenon compared with earlier eras. The number of days of therapy in a prescription has generally increased over time. Generic penetration rates are typically highest and most rapid for TPPs, and lowest and slowest for Medicaid. Cash customers and seniors generally pay the highest prices for brands and generics, third party payers and those under 65 pay the lowest prices, with Medicaid and Medicare Part D in between. The presence of an authorized generic during the 180-day exclusivity period has a significant impact on prices and volumes of prescriptions, but this varies across molecules.

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I. INTRODUCTION AND BACKGROUND

Since the early 2000s large numbers of brand name prescription drugs have lost the exclusive right to sell their products due to patent expiration and challenges. This loss of exclusivity (LOE) resulted in substantially lower prices for payers and consumers and reduced revenues for brand name prescription drug manufacturers. Compared with the 1980s and 1990s, the speed with which generics have gained market share from brands following LOE has accelerated.¹ Research has investigated market responses to LOE by examining generic entry, focusing on the rate at which generics are substituted for brands², the path of prices (generic, brand and molecule) paid,³ total (brand plus generic) molecule utilization following LOE,⁴ the relationship between number of generic manufacturers entering markets and prices, and trends in the duration of market exclusivity prior to initial LOE⁵, among other issues.⁶

In recent years the policy debate related to LOE in the U.S. has centered on provisions in the Hatch-Waxman Act that govern entry of generics. Most recently these provisions have figured prominently in the 2013 Supreme Court ruling on “pay for delay”. Under the Hatch-Waxman framework, generic drug companies have increased the rate at which they file so-called Paragraph IV challenges to the patent position of originator companies, either contesting the validity of the patents that protect brand name products or claiming that their version of the drug does not infringe them. .The substantial number of these challenges is in large measure due to the strong incentives created by the provision of the Hatch-Waxman Act that grants a 180-day period during which the successful challenger is the exclusive seller of the generic. In these circumstances, the generic may be able to win substantial market share from the brand with only a modest discount off the brand price, though it is important to note that the substantial profits that can accrue to the generic during this period may be reduced by additional competition from the brand that has the right to contract with a generic manufacturer to

market a so-called authorized generic product.⁷ In fact launching an authorized generic in the face of challenges from a generic manufacturer has become a widespread industry practice.⁸ Following the 180-day limited competition (duopoly with brand and exclusive generic, or triopoly with an additional authorized generic entrant), unfettered competition emerges, typically characterized by extensive generic entry and sharp price declines. In such situations the generic penetration and price reductions during the first 180 days following LOE can differ substantially from subsequent generic price and quantity movements when generic entry is unfettered.⁹

We extend and expand upon this literature by comparing the magnitude of quantity movements with the size of price reductions during and after the 180-day exclusivity period. We do so by carefully examining six molecules facing initial LOE between June 2009 and May 2013 that were among the fifty most prescribed molecules in the US in May 2013. We focus on retail rather than wholesale prices, and are able to disaggregate buyers in the overall retail market and separately examine the relative price and quantity movements before and following LOE for four distinct payers: Medicaid, Medicare Part D, commercial and other third party payers (TPPs), and cash customers. Relatively little is known about retail price and quantity movements during the 180 day exclusivity period¹⁰, or about the magnitude of any differences by payer type in prices paid, and the in the speed and extent of shifts from brand to generic. Finally, since information is available on the age of customers receiving medications, we examine relative prices and generic substitution rates for those under age 65 with those age 65 and older. We are not aware of any published research that examines these brand and generic price and quantity movements following LOE by payer type and patient age.

Our analyses yield the following main findings. First, quantity substitutions away from the brand are much larger proportionately and more rapid than average molecule price reductions during the first six months following LOE. Second, brands continue to raise prices after generics enter. Third, expansion of total molecule sales (brand plus generic) following LOE is an increasingly common phenomenon

compared with prior observations. Fourth, generic penetration rates are generally highest for third party payers and lowest for Medicaid. Fifth, cash (and seniors over age 65) generally pay the highest prices for brands and generics, third party payers (and those under age 65) pay the lowest prices, with Medicaid and Medicare Part D prices being in between those of cash and third party payers. Sixth, the presence of an authorized generic during the 180-day exclusivity period has a significant impact on prices and volume of prescriptions, but this varies across molecules. In two of the cases studied, the brand and its licensee collectively retained almost two-thirds share of the market by volume, in the others they captured less than half. Price discounts off the brand prevailing during the “triopoly” period also showed substantial variation. In some cases, the price of the authorized generic product was between the brand and the independent generic, in others it was significantly below the independent generic.

II. DATA AND METHODS

The IMS Health Incorporated National Prescription Audit (NPA) data base tracks prescriptions dispensed at a nationally representative sample of retail, mail order and long term care pharmacies and is projected to an estimate of total national prescriptions dispensed through these pharmacies on a monthly basis. We limit our analysis to prescriptions dispensed at retail pharmacies, and focus on the 50 most prescribed molecules (measured by number of prescriptions dispensed during May 2013). For each of these molecules, data are available on the distribution by payer type: Medicaid, Medicare Part D, commercial or other third party payer, and cash; for about half the transactions, information is also available on the age of the patient dispensed the prescription: 65 and over, or under age 65.

These NPA data reflect the perspective of the retail pharmacy, and prices measured at this point in the distribution chain correspond to the retail prices that the U.S. Bureau of Labor Statistics attempts to measure in constructing its monthly Consumer Price Index for Prescription Drugs.¹¹ The total revenue received by the dispensing pharmacy is the sum of the customer’s copayment or coinsurance

contribution, plus the amount (if any) reimbursed the dispensing pharmacy by the third party payer – Medicare Part D insurer, Medicaid, or commercial or other third party payer. This pharmacy price therefore includes reimbursement for the active pharmaceutical ingredient, a dispensing fee, and any customer copayment or coinsurance contribution. If the customer presents the pharmacy with a coupon, the value of that coupon is attributed to the patient copayment or coinsurance contribution; how well the NPA is able to capture coupon transactions is not publicly known. For our purposes, however, it is important to note that this pharmacy price already includes margins realized by wholesalers, pharmacies and any other distributors, and is therefore generally larger than the price (net of rebates and discounts) received by the brand and generic manufacturers. These rebates and discounts can be substantial, in some cases larger than the amount that consumers actually pay.¹²

Starting from the 50 most prescribed molecules in May 2013 we used information from the FDA's Orange Book to identify the six of these molecules that faced initial LOE during the June 2009 – May 2013 time period.¹³ For each of the six molecules, we identified NDC codes of the brand's strengths/formulations, and monthly number of prescriptions dispensed by payer type (Medicare Part D, Medicaid, third party commercial payer, and cash customer) and customer age (number under age 65, age 65 and over, and age unknown), average customer copayment/coinsurance contributions, and mean reimbursement to the pharmacy by third party payer. Similar monthly data were obtained for generic and authorized generic versions of the strengths/formulations of the molecule. The National Drug Codes (NDCs) of authorized generics were identified, and were alternatively treated separately or combined with NDC codes of abbreviated new drug application (ANDA) holders. Data on the mean number of extended units (EUs, e.g., tablets, capsules) per prescription along with recommended daily dosing data from the Drugs@FDA website were used to convert average price per prescription to average price per day of therapy (only Augmentin XR differed from once-daily dosing, with its recommended dosing being twice daily for 7-10 days). These NDC-specific average data were then

aggregated up to the molecule level separately for brands, generics and authorized generics, by payer type and customer age, using relative number of prescriptions by NDC code as weights.

III. FINDINGS: CHARACTERISTICS OF SIX INITIAL GENERIC LAUNCHES, JUNE 2009-MAY 2013

The most salient characteristics of the six molecules are summarized in Table 1, in chronological order by date of LOE from left to right. When originally approved by the FDA as New Drug Applications (NDAs), three of the six were new molecular entities, whereas the other three were new formulations of a previously approved molecular entity. Four of the six were designated standard review by the FDA, and two were tagged for priority review. The six molecules are in six different therapeutic classes, and represent five different original NDA holders (Sanofi Aventis is the only multiple NDA holder at two). Effective market exclusivity (time between initial NDA approval and first ANDA entry) varies substantially among the six molecules—from about 5.5 years for Ambien CR to about 15.0 years for both Cozaar and Lipitor. Although all six derive from the 50 most prescribed molecules, because several are new formulations of an older molecule, the market size (measured by total number of monthly prescriptions) varies dramatically. Specifically, for the three months prior to initial LOE, the market size (“Mean TRX Before LOE” in Table 1) varied from largest (Lipitor – atorvastatin) to smallest (Augmentin XR – amoxicillin/clavulanate potassium) by a factor of 1251:1; market size of the second largest (Plavix – clopidogrel) relative to second smallest (Ambien CR – zolpidem tartrate) varied by a factor of 4.66:1, while the market size of the third largest (Lexapro – escitalopram oxalate) relative to the third smallest (Cozaar – losartan) was 2.33:1. Hence, even though the sample of six molecules is small and comes entirely from among the 50 most prescribed molecules, the variation in market size of the molecular formulations in our sample is large.

All six brands faced successful Paragraph IV challengers, although because of its infringing pre-patent expiration entry, Apotex forfeited its 180-day exclusivity for Plavix (clopidogrel). As a result, Plavix was the only brand to face unrestricted generic entry at the time of its LOE. Of the remaining five

molecules, following LOE four of the brands (Cozaar, Ambien CR, Lipitor and Lexapro) launched authorized generics thereby creating a triopoly market for 180 days, while the remaining brand (Augmentin XR) did not launch an authorized generic and thereby faced duopoly competition between brand and generic for 180 days. By seven (twelve) months after initial generic entry, the molecule with the smallest pre-patent expiration market size that also involved complex manufacturing processes, (Augmentin XR) had just two (two) competitors, a reformulated extended release molecule with modest pre-patent expiration market size (Ambien CR) had four (five) competitors, while the molecule with the largest pre-patent expiration market size (Lipitor) had only six (seven) competitors. Three other molecules (Cozaar, Lexapro and Plavix) each had 13 or 14 competitors at both seven and twelve months following initial ANDA entry.

A more detailed discussion of each of the six molecules, in chronological order of initial ANDA launch, is provided in the Appendix.

IV. RESULTS

We now discuss results, in separate sub-sections for generic penetration rates by payer type and age; quantities post-LOE relative to pre-LOE; number extended units per prescription; prices by payer type pre-LOE, during any 180-day exclusivity periods, and post-180-day exclusivity; as well as prescription shares and prices for brands, Paragraph IV challengers and authorized generics (AGs) during the 180-day exclusivity period.

A. GENERIC PENETRATION RATES, OVER ALL AND BY PAYER TYPE AND AGE

We compute the generic penetration rate as the proportion of all prescriptions for a given molecule dispensed as generics (or authorized generic). With six molecules, five payer types and two age groups, the number of quantitative findings is voluminous. As an overview, we first ask, how long in number of months does it take for a molecule to reach certain specified generic penetration thresholds?

Results for 60% and 90% generic penetration thresholds are presented in Table 2. A number of findings are striking.

First, looking at the six molecules over all payer types, we observe that for all six drugs, the time required to reach a 60% generic penetration threshold is three months or less. A 60% generic penetration threshold was reached in one month or less by Lexapro, Plavix, Cozaar and Lipitor (<1 month is interpreted as the average generic penetration in the first month of entry exceeding 0.6); for the two smallest market drugs, Augmentin XR and Ambien CR, the 60% threshold over all payer types was two and three months, respectively. The 90% threshold for all payer types is attained within two months for Plavix (that faced unfettered generic entry throughout), four months for Cozaar and Augmentin XR, six months for Lexapro, and nine months for Lipitor; only for Ambien CR is the 90% threshold more than a year (13 months). This very rapid shift from brand to generic following LOE is much greater than has been reported in earlier US studies.¹⁴

A second set of findings in Table 2 reflects difference in the speed of generic penetration by payer type. Looking at the four payer types and over all payers within each molecule (the top row in each panel), we see that for all six molecules, third party payer (TPP) is always the most (or tied for most) rapid in reaching the 60% generic penetration threshold, whereas Medicaid is the slowest. To reach the 90% generic penetration threshold, in all cases but one (Lipitor, Medicare), TPPs take the shortest amount of time, followed by Medicare, cash customers, and finally, Medicaid. The relative speed with which TPPs reached high generic penetration thresholds could reflect in part aggressive formulary management by pharmaceutical benefit managers (PBMs) working on behalf of TPPs and Medicare Part D prescription drug plans. Other researchers have noted the relatively slow generic take-up by Medicaid and have leveled criticism at the program for failing to exploit available cost savings (e.g., Brill [2010].) It is worth noting, however, that manufacturer rebates to Medicaid from brands are several times larger than those from generic manufacturers (currently on average about 30+% for

brands having recent price increases vs. 13% for generics)¹⁵, and during the first few months following LOE in which there is only limited competition (say, at the beginning of the 180-day exclusivity period), it is possible that net of rebates, prices to Medicaid may be lower for brands than generics, thereby rationalizing a slower speed of generic substitution by the Medicaid programs. Recall that the prices we measure here are the total consumer plus third party payer payments to retail pharmacies, not prices net of rebates paid by payers or received by generic manufacturers. The lower brand than generic price net of rebates to Medicaid is not just a theoretical possibility. In their evaluation of state Medicaid program responses to Prozac's (fluoxetine) LOE in August 2001, Kelton, Chang and Kreling [2013, p. 1207] report that during 2001Q3 – the first full quarter in which generic fluoxetine was available – net of estimated Medicaid rebates the average price of a 20 mg tablet/capsule of branded Prozac at \$1.91 was slightly less than the average price of a 20 mg tablet/capsule of generic fluoxetine at \$1.95.

A third set of results in Table 2 is a negative finding: Evaluated at either the time required to reach a 60% or 90% generic penetration threshold, over all payer types those under age 65 take on average about the same length of time to reach the 60% generic penetration as do senior citizens age 65 and over; for the 90% threshold over all payers, for three of the six drugs seniors substitute more rapidly, and for one more slowly, than do those under age 65; for the other two drugs the switching speed is the same. Moreover, when one examines time to reach thresholds across payer types, there does not appear to be any dominant pattern for seniors vs. those under age 65.

The patterns observed in Table 2 suggest that consumers take FDA judgments about interchangeability at face value and benefits managers make policies independent of clinical or demographic circumstances. We note in passing because TPPs often manage prescription drug benefits for both employees and retirees age 65 and over, and because Medicare beneficiaries include some individuals under age 65 (e.g., End-Stage Renal Disease beneficiaries and most dually eligible

beneficiaries), there is a considerable overlap between prescriptions paid for by Medicare and those dispensed to customers age 65 and over.

Finally, the extent and speed of generic penetration in the single case with 180-day exclusivity but no authorized generic -- Augmentin XR -- appear to be a bit less aggressive and rapid than for Cozaar, Lexapro, and Lipitor (but not for Ambien CR), each of which had an authorized generic during its 180-day exclusivity period; Cozaar, Lexapro and Lipitor reached the 60% threshold in one month or less, whereas Augmentin XR and Ambien CR needed two-three months. With no 180-day exclusivity and unfettered generic entry at patent expiry, Plavix reached the 90% generic penetration threshold in the shortest amount of time -- two months.

B. QUANTITIES POST-LOE RELATIVE TO PRE-LOE

For quite some time it has been conventional wisdom that total brand plus generic utilization of a molecule declines following patent expiration.¹⁶ This is in large part because brands reduce their marketing as the date of patent expiration and initial loss of exclusivity (LOE) approaches. They then tend to terminate almost all marketing efforts immediately following LOE. As reported by Aitken, Berndt and Cutler [2008], however, this is not always the case. When the statin Zocor went off-patent in 2006, payers and PBMs aggressively switched individuals taking the relatively costly statin brand drug Lipitor (still under patent protection) to generic versions of Zocor (simvastatin), and also initiated new patients on simvastatin instead of Lipitor. We now examine whether the Zocor experience is unique or has become more common. Results are presented in Table 3, for average utilization six to nine months post-LOE relative to the three months pre-LOE, and for 10-12 months post-LOE relative to the three months pre-LOE, over all payer (buyer) types and both age groups. A number of results are worth noting.

First, for four of the six molecules, over all payer types, the total molecule utilization at both six-nine and ten-twelve months post-LOE is greater than during the three complete months prior to LOE. For one of the molecules (Plavix-clopidogrel) total molecule utilization is essentially flat, whereas for one

other molecule (Ambien CR – zolpidem tartrate) there is a very slight reduction in total molecule utilization post-LOE across all payer types. The reason for post-LOE total molecule utilization being so large for Augmentin XR is unclear to us, but we note from Table 1 that the number of monthly prescriptions in the three complete months pre-LOE was very small for Augmentin XR.¹⁷

Second, considerable variation occurs among payer types. Notably, in the four cases when post-LOE total molecule utilization increases, the increase is driven primarily by TPP payers (although for Lipitor cash and Medicare customers are also large drivers of increased molecule utilization). This is consistent with the large shift to generics and the substantial reduction in average molecule price that results. The smallest utilization increase or largest decrease occurs for Medicaid payers. In the one case where total molecule utilization decreases slightly post-LOE (Ambien CR), it is Medicare and Medicaid prescriptions that decline most post-LOE. Since we observed that Medicaid is generally the slowest payer to switch from brand to generic, the relatively large reductions post-LOE by Medicaid payers suggests they are not staying with the brand, but rather are either discontinuing treatment with that molecule altogether or are instead switching to another molecule, either brand or generic. This issue merits further examination.

Table 3 shows that in all four cases in which 10-12 months post-LOE total molecule utilization increased, total molecule utilization by cash customers increased. Note that because certain retail chains such as WalMart and Target introduced \$4 prescriptions for 30 days and \$9.99 prescriptions for 90 days, customer out-of-pocket cash payments for these prescriptions were likely less than the typical copayment or coinsurance customer contribution to the pharmacy for a first-tier generic drug under a private or public insurance plan formulary arrangement. While this shift to box merchandiser pharmacies might explain some of the growth in cash payer total molecule utilization, because Medicaid beneficiaries typically have very low if any copayment for first tier generic drugs, the shift to box merchandiser pharmacies is unlikely to be the source of the post-LOE decline in Medicaid total molecule

utilization. Alternatively, price declines to the uninsured may generate more demand response for the molecule than do price declines to an insured population. The extent to which the increase in utilization can be decomposed into increased demand from existing patients (through better compliance) versus demand from new patients, for example those that switch in to a newly genericized molecule from another branded molecule, is unclear and also merits further analysis.

Third, there is considerable heterogeneity among the five molecules having a 180-day exclusivity period. For Augmentin XR having no authorized generic entry, and for Ambien CR -- both extended release reformulations -- the post-LOE utilization experiences are dramatically different, with Augmentin XR showing a very substantial increase and Ambien CR a slight decline. While the other three molecules having an authorized generic present during the 180-day exclusivity each experienced a post-LOE total molecule utilization increase, the extent of this increased utilization varied considerably -- being largest for Cozaar, followed by Lipitor and then Lexapro.

Finally, regarding total molecule utilization post- vs. pre-LOE by age group, as seen in the final columns of Table 3, there is no striking pattern. In most but certainly not all cases, those under age 65 increase more or decrease less in their total molecule utilization than do those age 65 and over six to nine months after LOE, but even this modest trend is mitigated at ten to twelve months after LOE.

C. NUMBER EXTENDED UNITS PER PRESCRIPTION

One of the strategies employed by PBMs has been to encourage beneficiaries to switch from obtaining 30-day prescriptions at brick and mortar retail pharmacies to ordering 90-day prescriptions via mail order. Such a switch has been accomplished in part by 90-day copayments being only twice as large as 30-day copayments, thereby reducing beneficiaries' per diem copayment amount. This strategy has been particularly attractive for maintenance medications that treat chronic diseases (i.e. taken each day indefinitely), but obviously is less practical for medicines needed immediately to treat acute conditions or episodes.¹⁸ In response to seeing reduced foot traffic in their brick and mortar stores from

this shift to 90-day mail order prescriptions, several retail pharmacy chains have begun offering copayment incentive schemes similar to those by the PBM mail order firms.¹⁹

One implication of this shift from 30- to 90-day prescriptions is that the number of extended units (EUs, e.g., tablets, capsules) per prescription is likely to have increased somewhat during our 48-month sample time period (June 2009 – May 2013). Since our data are limited to retail pharmacy dispensing and excludes mail order, we expect this increase in number of EUs per Rx to be modest. However, we also expect that the extent to which prescriptions contain more EUs per prescription will vary among the six molecules in our sample since they are in six distinct therapeutic classes of medicines. A consequence is that the average price per prescription not taking into account shifts in the number of EUs per Rx could give a misleading picture of prescription drug per diem price changes over time. Therefore, before presenting results on price differences among payer types and age groups, we digress and first examine trends among our six molecules on number of EUs per Rx.

Due to space limitations, we do not present detailed results on EUs per Rx here; detailed figures can be accessed at the IMS Institute for Healthcare Informatics website. Our principal findings on number of EUs per Rx can be summarized as follows. For all molecules except Augmentin XR, the number of EUs per Rx increased over time, with the largest increasing being from about 39 to 45 for Cozaar. For Augmentin XR with twice daily dosing recommended for 7-10 days, while the number of EUs per Rx for the branded version increased from about 32 to 38 (16 to 19 days' supply), for the generic version it declined from 36 to 32 (18 to 16 days' supply). The smallest number of EUs per Rx occurred with Ambien CR prescriptions, for whom the increase during the sample time period was from almost 29 to just under 31 EUs per Rx. We conclude that while there is heterogeneity in EUs per Rx across the six molecules, the additional variability over time implies that it is preferable to measure trends in price per day of therapy rather than price per prescription.

D. PRICE PER DAY OF THERAPY BY PAYER TYPE

Price per day of therapy by payer type for the six molecules over the June 2009 – May 2013 time period are graphed in the six panels of Figure 1; the solid vertical red line denotes the date of initial LOE, while the dotted red vertical line represents 180 days later, corresponding with the expiry of any 180-day exclusivity (except for Plavix). Several results in Figure 1 merit special attention.

First, although the decline in average molecule price per day of therapy at the time of initial LOE is evident for all molecules, the price drop is most dramatic for Plavix (clopidogrel), for which generic entry at the time of LOE was unfettered, resulting in price per day of therapy falling from about \$6.50 to about \$3.50 (46%) within a month after initial LOE.

Second, we see important differences in prices across different classes of payers. We treat these cautiously, given the potential for differences in the level of unobserved rebates received by different classes of payers. (Recall that our price measure is from the perspective of average revenue per Rx received by the pharmacy, which does not include manufacturers' rebates to Medicaid and other payers; net of such rebates, Medicaid price premia might be much smaller, and perhaps may even be non-existent.) Nonetheless, it is interesting to note that both pre-LOE and during the 180-day exclusivity window, cash payers paid the highest prices, TPPs the lowest price, with Medicaid and then Medicare Part D in between. Price differences among payer types generally tended to decline over time, and by the end of the sample time period (May 2013) cash payers paid the highest prices for four of the six molecules (Ambien CR, Augmentin XR, Lexapro and Plavix), while Medicaid paid the highest prices for Cozaar and Lipitor. For Lipitor, the average price per day of therapy for Medicaid at just under \$3 was about twice that paid by TPPs.

Third, an intriguing phenomenon we observe in Figure 1 is that while at the time of initial LOE there is a noticeable immediate price decline, for Cozaar, Ambien CR, Lipitor and Lexapro – each of which was in a triopoly market structure including an authorized generic during the 180-day exclusivity

period – the average price per day of therapy is relatively flat during the remainder of the 180-day exclusivity window, and then (except for Ambien CR) falls sharply immediately following expiry of the exclusivity window. Somewhat counter-intuitively, the post-LOE price decline is larger and more sustained for Augmentin XR – in a duopoly market structures with no authorized generic entrant during the 180-day window. Why a three-competitor market structure generates higher and more stable prices than does a duopoly runs counter to basic economic intuition and merits further analysis.²⁰ In particular, future research might focus on the role played by the brand and its authorized generic agent in creating price discipline during the 180-day exclusivity window.

Finally, although we do not present price trends per day of therapy separately for those under age 65 and age 65 and over, we find there do not appear to be systematic differences paid per day of therapy by age group, and that any differences are relatively small in magnitude.

What is clear, however, in comparing quantity data in Tables 2 and 3 with price trends in Figure 1 is that even though the price reductions in the 180 days immediately following initial LOE are significant, they are much smaller and slower than the very dramatic increases in generic penetration rates, i.e., for these prescription drugs, following LOE quantities move much more quickly and proportionately than do prices.

E. PRICES AND PRESCRIPTION SHARES DURING THE 180-DAY TRIOPOLY

In Table 4 we present means (and standard deviations) of price per day of therapy and prescription shares during the four 180-day triopolies we observe in our data set (Cozaar, Ambien CR, Lipitor and Lexapro) in which not only does the brand face a successful Paragraph IV challenger, but it also launches an authorized generic (AG) that both competes with and contributes revenues to the branded franchise. Although our sample size is but four molecules, and any results should therefore be viewed as tentative requiring confirmation with a larger data set, several preliminary results are worth noting.

First, in terms of maintaining market share in the face of LOE, Sanofi's experience with Ambien CR and Pfizer's experience with Lipitor stand out. As seen in the bottom three panels of Table 4, while for both Cozaar and Lexapro the mean brand share during the triopoly falls to about 15%, at 44% and 40%, respectively, the Ambien CR and Lipitor brand shares were much larger; in addition, while the AG share for both Cozaar and Lexapro was about 35%, for Ambien CR and Lipitor it was just under 25%. An implication is that when one sums the prescription share for the brand plus that of its authorized generic, for both Cozaar and Lexapro this comes to about 50%, whereas for Ambien CR and Lipitor it soars to 65-68%.²¹ For the successful Paragraph IV challenger, therefore, while being able to capture approximately 50% of prescriptions during the triopolies involving Cozaar and Lexapro, during Ambien CR's and Lipitor's 180-day exclusivity period, Actavis Elizabeth and Ranbaxy – the independent non-authorized generic entrants -- only garnered about 35% of prescriptions. Industry analysts have suggested that Pfizer was able to secure this substantial share by giving payers, mail order firms and pharmaceutical benefit managers (PBMs) large rebates, aggressively marketing \$4 copay coupons in print media, and maintaining and perhaps even increasing direct-to-consumer marketing efforts before LOE and during the 180-day exclusivity period.²² We have no information regarding whether Sanofi undertook similar actions to protect its brand and authorized generic shares during the Ambien CR exclusivity period. Whether the more recent Lipitor experience remains historically unique or instead ushers in a new form of triopoly competition remains to be seen; the only other major brand facing initial LOE since the 2011-2012 Lipitor LOE was Plavix, but as noted earlier, because Apotex forfeited its Paragraph IV exclusivity, Plavix faced unfettered generic entry at the time of its initial LOE later in 2012 rather than a triopoly market structure.

A second set of findings (in the top panels of Table 4) involves revenues or average prices (any patient copayment plus third party payer reimbursements) received by retail pharmacies. Here the outlier drugs are Cozaar and Ambien CR, not Lipitor. For both Lipitor and Lexapro, the AG average price

is in between that of the brand and the generic (the successful Paragraph IV challenger), whereas for Ambien CR and Cozaar the AG average price is even lower than that of the generic; this latter phenomenon of AG retail prices being lowest was reported by the Federal Trade Commission [2011, ch. 3], but our finding based on more recent data of the independent generic average price being the lowest is novel. In all four cases, however, the brand has the highest price, being 25-30% higher than the generic except in the cases of Ambien CR and Cozaar where the brand-generic premium ranges between about 15-22%. It is worth emphasizing again that the prices measured here are those recouped by the retail pharmacy, and not the prices at which they acquire drugs from generic manufacturers (which are typically much lower).²³

F. CASH VS. FULL SAMPLE AVERAGE PRICE LEVELS AND GROWTH RATES

Our final set of analyses involves examining relative price levels and growth rates of prescriptions paid for by cash in comparison to the full sample of retail dispensed prescriptions. Several outcomes are plausible. One line of reasoning is that because cash customers must pay the full price of the drug, cash purchasers must value the prescription at a relatively high level, and knowing this, pharmacies can exploit this fact by charging cash customers higher prescription prices. A related view is that cash customers are less informed and cannot move market share across products, whereas benefit managers for third party payer insurers are more knowledgeable concerning alternative treatments for various conditions, and can use this knowledge and bargaining power to obtain lower prescription prices from pharmacies. An alternative view is that cash customers will be on average more price sensitive, and therefore will seek out those pharmacies advertising discounted prescriptions, such as the mass merchandiser pharmacies, thereby paying lower prices than those with insurance. While these views have diverse predictions for relative price levels paid by insured vs. the uninsured, without additional assumptions they make no predictions on relative growth rates of prescription prices for cash vs. insured customers.

To measure mean price growth rates, for each molecule we compute the average of log $[P(t)/P(t-1)]$ over the selected time interval, which for relatively small price changes such as that observed with our monthly data, yield results that can be interpreted as the mean percent growth rate in price.

In the top row of each of the six drug molecule panels in Table 5, we present mean cash/full sample prices (standard deviations in parentheses) over the full 48-month June 2009 – May 2013 sample time period, and then for three sub-periods: pre-LOE, during the 180-day exclusivity, and post-180 day exclusivity. In the case of Plavix, there was no 180-day exclusivity and we therefore present relative cash/full sample prices for only the pre-LOE and post-LOE time periods where generic entry is unfettered by any exclusivity. Several results are worth highlighting.

First, for all six molecules prices paid by cash customers are generally greater than those for the full sample. Over the entire 48-month time period and six molecules, the average cash price premium is about 17%, ranging from 11% for Lipitor to 24% for Augmentin XR. In the pre-LOE time periods, cash prices for brands are on average about 16% greater than for the full sample, and this cash price premium grows slightly to about 18% during and following 180-day exclusivity. There is remarkable little variability in the cash price premium during the 180-day exclusivity window (small standard deviation), and generally (except for Augmentin XR) considerably more variability following unfettered generic entry in the post-180 day time frame.

While results on relative price levels are quite robust and unambiguous, for relative growth rates our findings are more nuanced. Looking at the pre-LOE column in Table 5, when we compare the mean log $[P(t)/P(t-1)]$ over the six molecules, we observe that cash prices increase on average about 0.0078 percent per month, very slightly greater than the full-sample prices that increase on average 0.0073 percent monthly, which when accumulated over 12 months results in cash prices annually growing at 0.6% more rapidly than full sample prices. During any 180-day exclusivity period, on average

cash prices fall slightly less rapidly (-0.0268 vs. -0.0294) than do full sample prices, but this inequality is reversed following any 180-day exclusivity or when unfettered generic entry occurs, during which time cash prices fall about 1.2% more rapidly (-0.0345 vs. -0.0228) than do full sample prices. This last result is consistent with the pricing strategies of the mass merchandisers such as WalMart that offer \$4 30-day or \$9.99 90-day prescriptions to their customers once unfettered generic entry occurs, typically lower prices than those available from chain and independent retail pharmacies. Finally, averaged over all six molecules and the entire 48-month time period, cash prices fall very slightly more rapidly (-0.0117 vs. -0.0097, a difference of -0.0020 per month, or about 2.4% annually) than do full sample prices. Hence, cash vs. full-sample differences in price levels are quite substantial though stable over time, but differences in the growth rates vary during exclusivity and LOE sub-periods, although in general these growth rate differences are relatively small, i.e. the cash price level premia are proportionately stable over time.

V. SUMMARY AND CONCLUDING REMARKS

The extent and rate at which generic drugs capture market share in U.S. retail drug markets as brands lose market exclusivity has increased sharply over the last decade. This heightened generic penetration has been particularly evident for third party payers (TPPs), and likely reflects the increased bargaining power derived from formulary design by pharmaceutical benefit management (PBM) firms serving TPPs' drug benefit plans. One implication of this phenomenon is that to the extent "reverse payment" or "pay for delay" settlements result in delayed generic entry, consumers are harmed immediately by not gaining access to lower cost medicines. The relatively large number of top-selling drugs facing initial loss of exclusivity (LOE) in the U.S. in 2012 and 2013 has been unprecedented, with the resulting patent cliff revenue losses for brands in 2012 alone approaching \$29 billion and contributing to an overall 1% decline in U.S. nominal pharmaceutical spending²⁴, but providing a temporary windfall for the profit margins of wholesalers, retail and mail order pharmacies. Whether

these recent impacts on pharmaceutical spending will be repeated is unclear, particularly since the total dollar revenues of brand drugs facing initial LOE in the next few years is expected to be considerably smaller than in 2012 and 2013.²⁵

For four of the six molecules experiencing initial LOE in our 2009-2013 time frame, total monthly molecule utilization post-LOE exceeded that prior to patent expiration, reflecting the combined effects of cross-molecule substitution, new patients gaining access to lower-cost medicines, and non-adherent patients resuming drug treatment. This post-LOE increase in molecule utilization runs counter to prior understanding of this market, and also likely reflects the increased formulary design policies by PBMs. An implication is that not only do patent protected brands need to worry about their own patents expiring, but their brand's revenues can also be adversely affected if a competitive brand faces initial generic entry, for the newly competitive generic molecule can steal market share. More generally, these post-LOE utilization increases are creating novel complexities in defining drug markets for antitrust and other litigation-related damage assessments.

Our data also document that the probability of a brand's patent being challenged by a potential generic entrant is now very high, continuing an aggressive litigation trend reported by the Federal Trade Commission [2011], that often results in the Paragraph IV first-filer being awarded 180-days of exclusivity. With their expected revenues being threatened, brands have responded by launching their authorized generic (AG), thereby creating a 180-day triopoly calm before the patent cliff storm, with competition among the brand, its authorized generic and the successful Paragraph IV challenger. In spite of only modest average molecule price reductions during this 180-day exclusivity period (much less than after it expires), the substitution of prescription quantities away from the brand is already very large. Since through its combined sales of the brand and its AG the brand franchise can moderate the revenue loss from LOE, the financial lure of generics being awarded 180-day exclusivity is decreased. However, the evidence we find, as has the Federal Trade Commission [2013, chapter 7], suggests that

the existence of an AG during the 180-day exclusivity period does not dampen the extent of generic entry post-exclusivity: on the 181st day following initial LOE, the number of generics competing with the brand and with each other tends consistently to be large, in our sample between seven and 14.

Whether Pfizer's relatively successful defense of Lipitor during the 180-day exclusivity period through the use of coupons, rebates and other discounts is an historical quirk or instead is a harbinger of future more aggressive attempts by brands to protect brand revenues as patents expire remains to be seen.

A novel set of findings we have reported here involves identifying separate retail prices by payer type – cash, Medicare Part D, Medicaid and other commercial TPP. Our results suggest that declines in retail prices follow the incentives to each payer to pursue policies that result in price declines. In particular, the slower decline in Medicaid prices following LOE may be more rational than previously thought. Three caveats are worth noting, however. First, the prices we calculate represent the average total revenue received by a retail pharmacy for a dispensed prescription, converted to price per day of therapy. This average revenue is the sum of any reimbursement the pharmacy receives from a private or public payer for a dispensed prescription, plus any copayment or coinsurance amount contributed directly by the patient at the point of sale. This average revenue, viewed from the perspective of the retail pharmacy, differs from and is likely considerably larger than the average acquisition cost of the drug the retail pharmacy pays wholesalers or manufacturers.²⁶ It also differs from the average revenue net of rebates and other discounts that is received by the manufacturer selling to wholesalers or providers, and the average amount per prescription contracted among payers, PBMs and manufacturers – in both these latter cases, rebates from the manufacturer to payers and PBMs make it likely that these other prices are lower than the average total revenue received by the retail pharmacy. Second, because the retail pharmacy average revenue price is not directly affected by rebates from manufacturers to public and private payers, the relative brand-generic prices that payers provide retail pharmacies might differ considerably once rebates from manufacturers to payers are taken into account. In particular, as

noted earlier, provisions of the Affordable Care Act of 2010 mandate that Medicaid receive a rebate of 13% off the average manufacturers' price (AMP) for a generic, and on average approximately 30+% discount off AMP for a branded patent-protected drug. Third, our sample is very small – six molecules each for 48 months, and thus these small sample findings cannot at this point be generalized to the entire U.S. retail pharmaceutical market (a similar analysis of a much larger sample is on our research agenda).

With these caveats regarding rebates and small sample size in mind, we find that in general the price levels paid retail pharmacies per day of therapy are highest for cash and Medicaid payers, and are lowest for other TPPs, with the cash price premium over TPP prices being on average just under 20%. In terms of growth rates, however, cash prices of patent protected molecules grow at virtually the same rate as overall market prices (the annualized difference being +0.06%), during 180-day exclusivity the cash prices fall slightly less rapidly than overall market prices, and post any exclusivity cash prices fall about 1% more rapidly per month than do overall market prices. Averaged over all six molecules and all 48 months, cash prices fall slightly more rapidly (about 2.4% annually) than do overall market prices. An implication of this is that if for administrative and logistical reasons statistical agencies such as the U.S. Bureau of Labor Statistics find themselves disproportionately reliant on cash transaction price quotes, the potential consequences for price mis-measurement are likely to be relatively minor. Establishing this last conclusion will be the focus of our immediate future research program.

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TABLE 1
CHARACTERISTICS OF SIX INITIAL GENERIC LAUNCHES, JUNE 2009 – MAY 2013
(IN CHRONOLOGICAL ORDER -- ANDA ENTRY DATE, LEFT TO RIGHT)

Trade Name Generic Name	Cozaar losartan	Augmentin XR amoxicillin/clavu- lanate potassium	Ambien CR zolpidem tartrate	Lipitor atorvastatin	Lexapro escitalopram oxalate	Plavix clopidogrel
NDA Approval	4/14/1995	9/25/2002	4/2/2005	11/17/1996	8/14/02	11/17/97
NME or New Formulation	NME	NF	NF	NME	NF	NME
Review Status	Standard	Standard	Standard	Priority	Standard	Priority
Therapeutic Class	AIIRA Anti- hypertensive	Aminopenicillin antibiotic	Insomnia	Antihyper- lipidemic	SSRI anti- depressant	Antiplatelet aggregation inhibitor
NDA Sponsor	Merck	Dr. Reddys Labs	Sanofi Aventis US	Pfizer	Forest	Sanofi Aventis US
Mean TRX Before LOE	634,846	2,281	371,580	2,854,162	1,485,203	1,730,464
Paragraph IV Challenger	Teva	Sandoz	Actavis Elizabeth	Ranbaxy	Ivax	Apotex (forfeited)
Initial ANDA Entry Date	4/6/2010	4/21/2010	10/13/2010	11/30/2011	3/14/2012	5/17/2012
Authorized Generic	Sandoz	Winthrop	None	Watson	Mylan	None
Max. No. Mfrs. during 1-6 Months	2	2	2	3	3	12
No. Mfrs. At 7 Months	14	2	4	6	14	13
No. Mfrs. At 12 Months	14	2	5	7	14	13

Notes: NF is new formulation; AIIRA is Angiotensin II Receptor Antagonists; SSRI is selective serotonin reuptake inhibitor; NDA Sponsor is patent holder at time of patent expiration; Mean TRX Before LOE is the mean monthly number of prescriptions dispensed in the three full months preceding loss of exclusivity.

TABLE 2

MONTHS TO GENERIC PENETRATION RATE THRESHOLDS, JUNE 2009 – MAY 2013

(IN CHRONOLOGICAL ORDER -- ANDA ENTRY DATE, TOP TO BOTTOM)

Trade Name Generic Name	Buyer Type	Threshold All Buyers		Threshold Under 65		Threshold Over 65	
		60%	90%	60%	90%	60%	90%
Cozaar losartan	All	1	4	1	5	1	3
	TPP	1	2	1	2	1	3
	Medicare	1	3	1	2	1	3
	Cash	1	9	1	7	1	9
	Medicaid	8	21	8	17	8	24
Augmentin XR amoxicillin/clavu- lanate potassium	All	2	4	2	4	2	4
	TPP	2	3	2	3	2	4
	Medicare	2	3	2	3	2	3
	Cash	2	9	2	9	4	5
	Medicaid	5	9	5	9	4	4
Ambien CR zolpidem tartrate	All	3	13	3	12	3	17
	TPP	3	10	3	10	3	14
	Medicare	3	20	3	20	3	23
	Cash	3	22	3	22	3	-
	Medicaid	10	-	10	31	16	27
Lipitor atorvastatin	All	1	9	1	9	1	8
	TPP	1	9	1	9	1	8
	Medicare	2	8	2	8	2	8
	Cash	1	10	1	10	1	11
	Medicaid	8	11	8	12	8	11
Lexapro Escitalopram oxalate	All	<1	6	<1	6	<1	5
	TPP	<1	4	<1	4	<1	4
	Medicare	<1	4	<1	3	<1	5
	Cash	<1	8	<1	8	1	9
	Medicaid	7	11	7	11	7	13
Plavix clopidogrel	All	1	2	1	2	1	2
	TPP	1	1	1	1	1	1
	Medicare	1	2	1	2	1	2
	Cash	1	3	1	2	1	3
	Medicaid	1	4	1	4	1	3

TABLE 3
QUANTITIES POST-LOE SIX TO NINE MONTHS, AND POST-LOE TEN TO 12 MONTHS,
RELATIVE TO PRE-LOE QUANTITIES, JUNE 2009 – MAY 2013
(IN CHRONOLOGICAL ORDER -- ANDA ENTRY DATE, TOP TO BOTTOM)

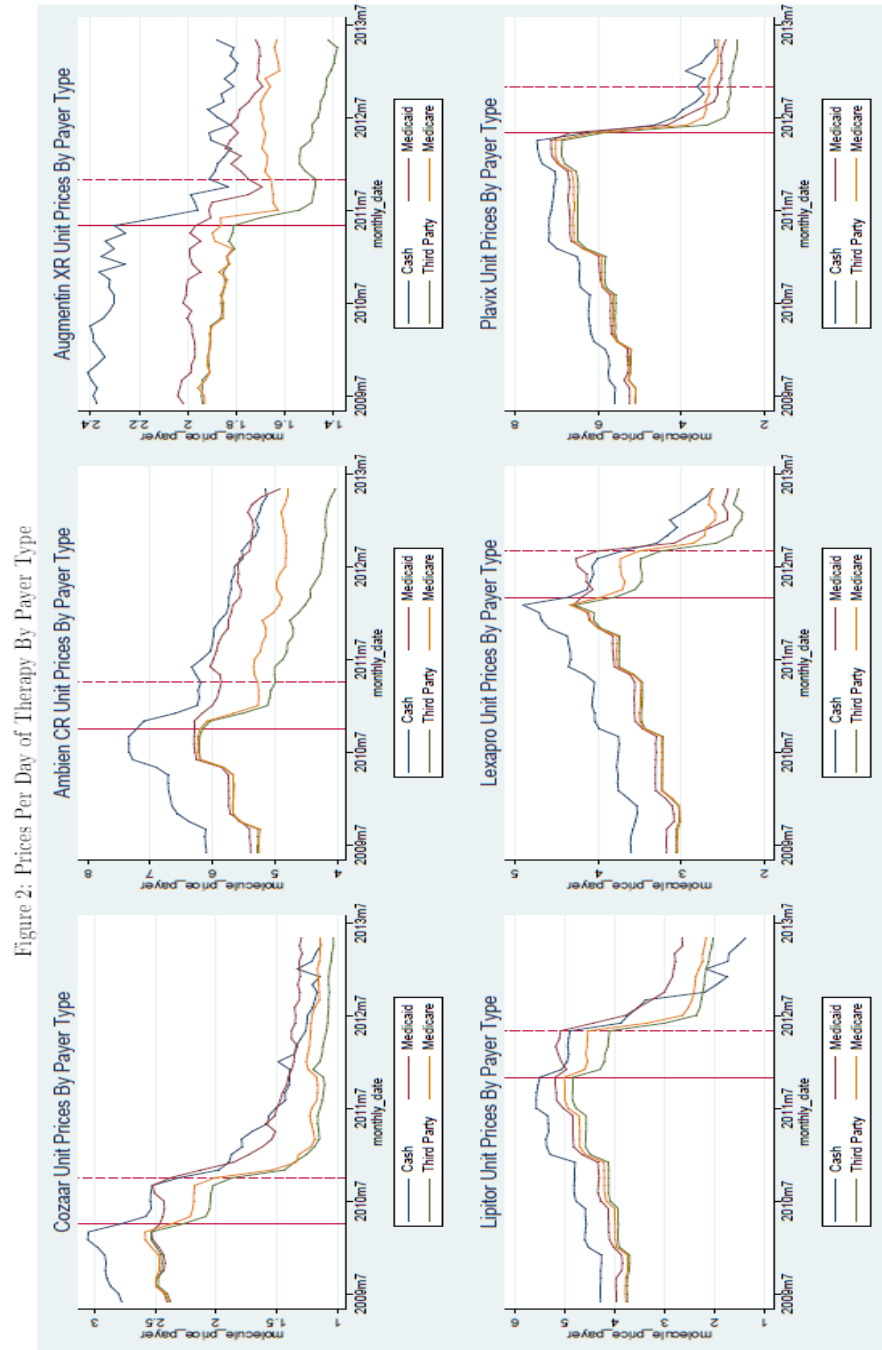
Trade Name Generic Name	Buyer Type	All Buyers		Under 65		Over 65	
		POST/PRE 6-9	POST/PRE 10-12	POST/PRE 6-9	POST/PRE 10-12	POST/PRE 6-9	POST/PRE 10-12
Cozaar losartan	All	1.60	1.86	1.67	1.89	1.54	1.81
	TPP	1.61	1.84	1.72	1.97	1.43	1.58
	Medicare	1.30	1.68	1.78	1.91	1.66	2.04
	Cash	1.40	1.59	1.57	1.80	1.23	1.37
	Medicaid	1.11	1.20	1.13	1.22	1.03	1.09
Augmentin XR amoxicillin/clavu- lanate potassium	All	4.52	4.68	4.50	4.55	4.59	5.17
	TPP	5.76	5.93	5.87	5.95	4.85	5.25
	Medicare	4.83	5.46	4.46	4.53	5.03	5.99
	Cash	2.82	2.94	3.09	3.09	1.78	2.06
	Medicaid	0.64	0.61	0.64	0.62	0.43	0.41
Ambien CR zolpidem tartrate	All	0.96	0.96	0.97	0.97	0.92	0.89
	TPP	1.00	1.00	1.00	1.00	1.00	0.97
	Medicare	0.77	0.78	0.85	0.87	0.71	0.70
	Cash	0.86	0.84	0.80	0.80	1.12	1.04
	Medicaid	0.80	0.73	0.81	0.74	0.62	0.52
Lipitor atorvastatin	All	1.24	1.31	1.25	1.35	1.22	1.24
	TPP	1.24	1.29	1.29	1.37	1.11	1.10
	Medicare	1.29	1.36	1.23	1.38	1.31	1.35
	Cash	1.40	1.89	1.34	1.88	1.49	1.90
	Medicaid	0.63	0.75	0.63	0.75	0.63	0.73
Lexapro Escitalopram xalate	All	1.09	1.14	1.11	1.15	1.01	1.08
	TPP	1.13	1.18	1.15	1.20	0.94	0.97
	Medicare	1.07	1.10	1.07	1.02	1.06	1.15
	Cash	0.92	1.12	0.93	1.12	0.90	1.16
	Medicaid	0.83	0.81	0.83	0.81	0.70	0.72
Plavix clopidogrel	All	1.00	0.98	1.05	0.99	0.98	0.97
	TPP	1.00	0.95	1.05	1.00	0.93	0.88
	Medicare	1.00	1.00	1.08	0.97	0.99	1.00
	Cash	1.60	1.45	1.62	1.56	1.56	1.35
	Medicaid	0.86	0.80	0.85	0.78	0.96	0.92

Variable/Molecule	Cozaar	Ambien CR	Lipitor	Lexapro
Mean (s.d.) Branded Price	2.55 (0.06)	6.27 (0.04)	5.13 (0.12)	4.49 (0.20)
Mean (s.d.) Generic Price	2.19 (0.07)	5.15 (0.35)	3.82 (0.44)	3.06 (0.14)
Mean (s.d.) Authorized Generic Price	1.86 (0.10)	4.46 (0.07)	4.46 (0.20)	3.99 (0.10)
Mean (s.d.) Branded Share	0.16 (0.14)	0.44 (0.36)	0.40 (0.27)	0.15 (0.07)
Mean (s.d.) Generic Share	0.50 (0.09)	0.32 (0.23)	0.36 (0.18)	0.48 (0.14)
Mean (s.d.) Authorized Generic Share	0.34 (0.05)	0.24 (0.16)	0.24 (0.12)	0.37 (0.07)

TABLE 5
CASH VERSUS FULL SAMPLE PRICE LEVELS AND GROWTH RATES
(STANDARD DEVIATIONS IN PARENTHESES)

Trade Name Generic Name	Measure	Full 48 Months	Pre LOE	During 180 Day	Post 180 Day
Cozaar losartan	Mean Cash/Full	1.19 (0.107)	1.17 (0.014)	1.20 (0.005)	1.20 (0.133)
	Log[P(t)/P(t-1)] Full	-0.017 (0.046)	0.007 (0.013)	-0.031 (0.039)	-0.011 (0.026)
	Log[P(t)/P(t-1)] Cash	-0.019 (0.048)	0.010 (0.011)	-0.032 (0.043)	-0.018 (0.047)
Augmentin XR amoxicillin/clavu -lanate potassium	Mean Cash/Full	1.24 (0.027)	1.23 (0.015)	1.25 (0.035)	1.23 (0.034)
	Log[P(t)/P(t-1)] Full	-0.006 (0.019)	-0.002 (0.007)	-0.035 (0.039)	-0.003 (0.010)
	Log[P(t)/P(t-1)] Cash	-0.005 (0.029)	-0.002 (0.019)	-0.031 (0.056)	-0.0002 (0.026)
Ambien CR zolpidem tartrate	Mean Cash/Full	1.21 (0.041)	1.16 (0.013)	1.18 (0.021)	1.24 (0.022)
	Log[P(t)/P(t-1)] Full	-0.005 (0.022)	0.011 (0.021)	-0.033 (0.035)	-0.008 (0.010)
	Log[P(t)/P(t-1)] Cash	-0.003 (0.020)	0.012 (0.018)	-0.026 (0.031)	-0.008 (0.010)
Lipitor atorvastatin	Mean Cash/Full	1.11 (0.157)	1.15 (0.009)	1.14 (0.011)	1.02 (0.303)
	Log[P(t)/P(t-1)] Full	-0.013 (0.061)	0.009 (0.021)	-0.023 (0.041)	-0.039 (0.064)
	Log[P(t)/P(t-1)] Cash	-0.024 (0.092)	0.009 (0.024)	-0.019 (0.032)	-0.093 (0.156)
Lexapro Escitalopram oxalate	Mean Cash/Full	1.16 (0.039)	1.16 (0.007)	1.13 (0.012)	1.21 (0.078)
	Log[P(t)/P(t-1)] Full	-0.005 (0.044)	0.010 (0.020)	-0.025 (0.034)	-0.016 (0.031)
	Log[P(t)/P(t-1)] Cash	-0.007 (0.036)	0.010 (0.018)	-0.026 (0.032)	-0.032 (0.028)
Plavix clopidogrel	Mean Cash/Full	1.11 (0.053)	1.09 (0.013)	-	1.17 (0.078)
	Log[P(t)/P(t-1)] Full	-0.012 (0.079)	0.009 (0.019)	-	-0.060 (0.140)
	Log [P(t)/P(t-1)] Cash	-0.012 (0.063)	0.008 (0.017)	-	-0.056 (0.010)

Figure 1 – Price per Day of Therapy



APPENDIX: BRIEF DESCRIPTION OF THE SIX MOLECULES IN THE DATA SAMPLE

Cozaar (losartan)

Two weeks after Cozaar, an antihypertensive, was approved by the FDA, Merck obtained FDA approval for Hyzaar, a combination product that contained Cozaar (losartan potassium) as one component and a very old off-patent beta blocker called hydrochlorothiazide as the other component. Teva successfully challenged a Merck patent underlying both Cozaar and Hyzaar, and was granted 180-day exclusivity effective April 5, 2010 and launched its product one day later. Merck contracted with Sandoz to launch an authorized generic version of Cozaar coinciding with the launch of Teva's generic Cozaar. On October 6, 2010 when 180-day exclusivity expired, massive generic entry occurred at all three Cozaar dosages, with 12 new ANDAs entering.

Augmentin XR (amoxicillin/clavulanate potassium)

Although GlaxoSmithKline (GSK) was the original NDA holder for Augmentin XR, a combination antibiotic product with amoxicillin – an old penicillin) and clavulate potassium as components, at the time of patent expiration in 2010, the NDA holder was Dr. Reddys Labs, Inc., a manufacturer best known as a generic manufacturer. According to Drugs@FDA, Sandoz is the only FDA-recognized ANDA entrant. Currently there are only two manufacturers (Dr. Reddy's Labs, Inc. and Sandoz). This may be explained by the relatively small market size (2,281 mean monthly prescriptions) and the complexity of manufacturing processes of the extended release version. Notably, the recommended use of this antibiotic is a twice-daily dosing for 7-10 days²⁷, implying that the recommended number of extended units in a typical single episode prescription (14-20) is smaller than for 30 or 90-day prescriptions of once daily maintenance medications (in effect an even smaller market than is implied by the prescription count).

Ambien CR (zolpidem tartrate)

Ambien CR is an extended release version of Ambien immediate release (Ambien CR has a pharmacokinetic activity that provides an immediate dose release to facilitate getting to sleep, but then provides a sustained release that facilitates a longer duration of sleeping). Sanofi Aventis US obtained FDA approval for Ambien CR about 18 months before the Ambien immediate release patent expiry. Actavis was granted 180-day exclusivity for the 6.25 mg formulation on October 13, 2010, while Anchen was awarded exclusivity for the 12.5 mg formulation on December 3, 2010. Winthrop, a subsidiary of Sanofi Aventis US, launched an authorized generic for each of the dosage forms within days of each exclusivity taking effect. Sublingual (under the tongue) and oral spray formulations at varying dosages are also available having different brand names Edluar, Intermezzo and Zolpimist, but they are not rated as therapeutic equivalents to Ambien CR by the FDA.

Lipitor (atorvastatin)

Perhaps the most highly publicized patent expiry in the last decade was that for Pfizer's Lipitor (atorvastatin), a drug controlling cholesterol lipids. Patents on all formulations were successfully challenged by Ranbaxy, who was awarded 180-day exclusivity on its ANDA on November 30, 2011 that expired May 28, 2012. However, Pfizer contracted with Watson (later Actavis)²⁸ to market an authorized generic version of all dosages, and also initiated an aggressive coupon program that reduced considerably the customer copayment typically required for branded drugs on the second or higher tier of a formulary.²⁹ During the exclusivity period, therefore, there were three competitors (Pfizer's brand, its authorized generic through Watson, and Ranbaxy) and on the day exclusivity expired, three additional ANDA holders entered at all four dosages (Apotex, Mylan and Sandoz). A notable feature of the Lipitor-atorvastatin patent expiry is that even though it had the largest pre-LOE market size, more than a year after the May 2012 unfettered ANDA entry, there are only five ANDA holders competing at each dosage strength; as seen in Table 1, for other molecules the number of ANDA holder entrants is

much larger, at 12-15 entrants. The small number of competitors in this market is curious – it may reflect the fact that the small number of approved ANDA holders are each known to have substantial manufacturing capacity, or that Pfizer’s highly publicized aggressive protection of its brand reduced the perceived payoff to entry by generic manufacturers.³⁰

Lexapro

Lexapro (escitalopram oxalate) is an antidepressant marketed in the US by Forest Labs; its NDA was approved as a new formulation (it is an isomer of the earlier Forest antidepressant drug Celexa – citalopram – both of which were licensed into Forest after being on the European market for a number of years). Ivax was awarded 180-day exclusivity effective March 14, 2012 for all three tablet versions. On the day after exclusivity expiration – September 11, 2012 -- a total of nine additional generic entrants came to market, each offering tablets at all three dosages, and the next day two additional entrants were launched, for a total of 12 generic manufacturers of escitalopram immediately following the exclusivity period.

Plavix

The launch of Plavix (clopidogrel) represented the culmination of contentious legal skirmishes among Sanofi, Bristol Myers Squibb (the US marketer of Plavix), Apotex and various states’ Attorneys General. Initial proposed settlements between BMS and Apotex allowing Apotex to have several months of exclusivity were rejected by the Attorneys General, and eventually Apotex acceded to forfeiting any rights to exclusivity. The Plavix patent finally expired on May 17, 2012, on which date with unfettered generic entry seven ANDAs launched at 75 mg and four at 300 mg; as of June 10, 2013, there appear to be 13 ANDA entrants at the 75 mg formulation, and six at the 300 mg dosage.

ENDNOTES

¹See, for example, Aitken, Berndt and Cutler [2008], Aitken and Berndt [2011], Berndt and Aitken [2011], and Generic Pharmaceutical Association [2012, 2013].

² Berndt, Cockburn and Griliches [1996], Caves, Whinston and Hurwitz [1991], Cook [1998], Ellison, Cockburn, Griliches and Hausman [1997], Ellison and Ellison [2011], Frank and Salkever [1992, 1997], Grabowski and Kyle [2007], Grabowski, Kyle, Mortimer, Long and Kirson [2011], Grabowski, Long and Mortimer [2011, 2013], Grabowski and Vernon [1992, 1996], Griliches and Cockburn [2004], Hurwitz and Caves [1998], Reiffen and Ward [2005], Saha, Grabowski, Birnbaum, Greenberg and Bizan [2006], Scott Morton [1999, 2000] and Wiggins and Maness [2004].

³ Cook [1998], Frank and Salkever [1992, 1997], Regan [2008], and Wiggins and Maness [2004].

⁴ Aitken, Berndt and Cutler [2008], and Caves, Whinston and Hurwitz [1991].

⁵ Grabowski, Kyle, Mortimer, Long and Kirson [2011], Grabowski and Kyle [2007], and Hemphill and Sampat [2012].

⁶ Other aspects studied include factors determining the extent and composition of generic manufacturer entry (Scott Morton [1999, 2000]), characteristics of molecules that impede or accelerate generic penetration (Grabowski, Long and Mortimer [2011, 2013]), differential therapeutic class composition between retail and mail order generic drug dispensing (Wosinska and Huckman [2004]), and variation among states with large public funded programs such as Medicaid in exploiting cost savings opportunities following the brand's LOE (Avalere Health LLC [2010], Brill [2010] and Kelton, Chang and Kreling [2013]).

⁷ Appelt [2013]; Berndt, Mortimer, Bhattacharjya, Parece and Tuttle [2007], Branstetter, Chatterjee and Higgins [2011]; Federal Trade Commission [2002, 2009, 2011], Grabowski, Kyle, Mortimer, Long and Kirson [2011], Hemphill and Sampat [2012], Olson and Wendling [2013], Panattoni [2011], and Wang [2012].

⁸ Federal Trade Commission [2011].

⁹ Appelt [2013], Berndt, Mortimer, Bhattacharjya, Parece and Tuttle [2007], Olson and Wendling [2013] and Reiffen and Ward [2007]. For a discussion of the implications of Paragraph IV challenges on consumers' and producers' welfare, see Branstetter, Chatterjee and Higgins [2011].

¹⁰ See, however, Federal Trade Commission [2011], ch. 3 and Alpert, Duggan and Hellerstein [2013].

¹¹ Berndt, Cutler, Frank, Griliches, Newhouse and Triplett [2000], and U.S. Department of Labor, Bureau of Labor Statistics [2011].

¹² Federal Trade Commission [2011] and Centers for Medicare & Medicaid Services [2012].

¹³ One brand product, Plavix (generic name clopidogrel), faced an at-risk launch by Apotex in August 2006; later that month Bristol Myers Squibb (the firm marketing Plavix in the US) obtained an injunction preventing further production and distribution by Apotex, and subsequently won a patent infringement case against Apotex. As the single non-brand entrant in the market for the three-week period, Apotex charged about 87% of the brand's price, but stuffed inventory channels with massive sales. Although Apotex had been awarded tentative Paragraph IV exclusivity, this exclusivity was forfeited by Apotex. By late 2007 Apotex's clopidogrel inventory had essentially disappeared from the US retail marketplace. We therefore treat the May 2012 launch of generic clopidogrel as the initial LOE for Plavix, and not the August 2006 at-risk launch by Apotex. Additional details are given in Berndt-Aitken [2011]; for a journalist's account of the Plavix – clopidogrel episode, see Smith [2007].

¹⁴ See, for example, Grabowski and Vernon [1992, 1996], Griliches and Cockburn [1994], Ellison, Cockburn, Griliches and Hausman [1997], Cook [1998], Aitken, Berndt and Cutler [2008], and Berndt and Newhouse [2012].

¹⁵ For the purpose of calculating Average Manufacturer's Price (AMP) and Best Prices that trigger Medicaid rebates, since 2007 the prices of authorized generics have been treated as brand prices, not generic (Federal Trade Commission [2011], p. 13 and Appendix J). For brands, in addition to the statutory 23.1% rebate, the extent to which the brand's current quarter AMP has exceeded growth in the Consumer Price Index-Urban since product launch is applied to the rebate, implying that for many brands, the total Medicaid rebate is above 30%. For non-innovator multisource drugs (independent generics), the rebate is 13% of AMP, with no adjustment for excess price inflation. See Medicaid Drug Rebate Program [2013].

¹⁶ See, for example, Berndt, Cockburn and Griliches [1996], Caves, Whinston and Hurwitz [1991], Cook [1998], Ellison and Ellison [2011], Grabowski and Vernon [1996], Hurwitz and Caves [1988], Huskamp, Donohue, Koss, Berndt and Frank [2008] and Regan [2008].

¹⁷ The number of Augmentin XR prescriptions in the three months pre-LOE displayed no growth pattern; the increase post-LOE represents a break in trend (results not shown).

¹⁸ Wosinska and Huckman [2004] discuss variations in the therapeutic class composition between prescriptions dispensed by retail versus mail order.

¹⁹ Trends in mail order vs. retail prescription copayment levels and coinsurance rates are discussed in Berndt and Newhouse [2012], pp. 241-48.

²⁰ For a preliminary theoretical analysis and empirical implementation based on data from the 1980s and 1990s, see Reiffen and Ward [2007].

²¹ When the authorized generic is launched by the subsidiary of the brand (e.g., Winthrop for Sanofi Aventis), the brand franchise captures all non-independent generic sales dollars. However, when the brand licenses out authorized generic marketing rights to an independent generic manufacturer, the brand franchise still benefits from royalties it receives from the independent generic manufacturer. In recent years, according to the Federal Trade Commission [2011, p. 85], this royalty rate has been 90% and above.

²² See, for example, Drug Channels [2012].

²³ Ibid. Also see Federal Trade Commission [2011, chs. 3 and 6] and Olson and Wendling [2013].

²⁴ IMS Institute for Healthcare Informatics [2013], pp. 8,12; FiercePharma [2012].

²⁵ Drug Channels [2011, 2012].

²⁶ For details, see Centers for Medicare & Medicaid Services [2012]; also see Drug Channels [2011, 2012].

²⁷ Drug Facts and Comparisons [2011], p. 2088.

²⁸ Pfizer entered into an authorized generic arrangement with a generic challenger (Arrow) on a separate patent dispute, and Arrow was subsequently acquired by Watson, which merged with Actavis.

²⁹ The coupon program was only available to cash or 3rd party patients in states that did not preclude use of coupons. Though highly visible and heavily promoted in mass media, the number of patients that participated in the program appears to have been quite small, likely well below 10% of those eligible.

³⁰ On the market's perception of the reputation of Pfizer and its generic subsidiary, Greenstone, see Federal Trade Commission [2011], p. 82.