IDEI Working Paper Series n° 702

March, 2012

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Impacts of Patent Expiry and Regulatory Policies on Daily Cost of Pharmaceutical Treatments: OECD Countries, 2004-2010

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Abstract: Cross-country variability in regulatory frameworks, industrial policy, physician/pharmacy autonomy, brand/generic distinctions, and in the practice of medicine contributes to ambiguous interpretations of pharmaceutical cost comparisons. Here we report cross-country comparisons that: (i) focus on 11 therapeutic classes experiencing patent expiration and loss of exclusivity 2004-2010 in eight industrialized countries; (ii) convert revenues and unit sales to cost per day of treatment and number patient days treated using the World Health Organizations' Defined Daily Dosage metrics; (iii) compare patterns in costs per day of treatment with price index measures based on average price per day of treatment for each molecule computed over all molecule versions; (iv) utilizing econometric methods, model and quantify various factors affecting variations in daily treatment price indexes such as national regulatory and reimbursement policy changes, physician/pharmacy autonomy, and other factors; and (v) simulate changes in expenditures by country and therapeutic class had counterfactual policies been implemented.

*MIT Sloan School of Management and National Bureau of Economic Research (ERB), and Toulouse School of Economics (PD). Research support from Merck & Co., Inc. and Pfizer Inc is gratefully acknowledged, as is data analysis by Michael Kleinrock at the IMS Institute for Healthcare Informatics. Analyses are based on data obtained under license from the IMS Health Incorporated MIDAS™ database. The opinions and views expressed herein are those of the authors, and are not necessarily those of the institutions with whom they are affiliated, or the research sponsors.

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Key Words: cross-country comparisons, pharmaceutical costs, generic drugs

JEL Classification: D4, I11, I18, L11, L65, O34

Word Count: Text 10,062; References 1,359; Appendices A & B 2,458; Endnotes 458; Total 14,337

I. INTRODUCTION AND BACKGROUND

Cross-country comparisons of various health care costs and prices have long been confounded by substantial differences across countries and time in the baskets of health care services and products consumed. Even when focusing on just one health care product component such as pharmaceuticals, research by Danzon and various coauthors has documented that *bilateral* relative pharmaceutical price comparisons across countries can be very sensitive to the choice of which country's quantity weights are utilized in the price index calculations.[1] While index number formulae have been developed for pooled cross-section time series *multilateral* price indexes (in which one region's price index depends on its own and all other regions' quantity weights), as Deaton and Heston [2010] have emphasized in the context of purchasing power parities, when substantial quantity weight differences exist both cross-sectionally and intertemporally, the interpretation of an hypothetical "base-region" becomes inherently ambiguous and uninformative. As a result, multilateral comparisons typically are anchored by specifying one region-time period as the base against which various bilateral comparisons are made. Owing perhaps to their inherent interpretive ambiguity, therefore, there is very little if any empirical literature on cross-country health care cost comparisons based on truly multilateral price indexes.

A much narrower focus can, however, be informative. In the context of pharmaceuticals, various researchers have examined generic efficiency rates (defined as, for a given chemical molecule, the proportion of all brand plus generic prescription units that are dispensed as generic), and how they evolve following loss of patent protection or other market exclusivity, along with variations across therapeutic classes and regions; the literature reports both within-country[2] and cross-country comparisons of generic efficiency rates and their evolution over time.[3] Factors identified as affecting variations in generic efficiency paths include: price controls that keep branded prices relatively low and thereby provide limited economic incentives for generic entry;[4] strategic efforts affecting barriers to generic entry, such as advertising, proliferation of "branded generics", line extensions, "evergreening",

patent challenges, and impact of parallel imports;[5] product liability provisions;[6] domestic industrial policy promotion and costs of generic entry (market approval fees, costs of bioequivalence and drug stability studies);[7] and the role of physicians vs. pharmacies in brand-generic decision-making.[8]

A related literature expanding beyond analyses of generic efficiency rates focuses on relative brand/generic prices, brand pricing following loss of market exclusivity, average molecule price across all brand and generic units prescribed following initial generic entry, and molecule-specific price indexes;[9] obviously, since prices and quantities are jointly determined, this pricing literature encompasses generic efficiency rates. A challenge facing these brand-generic analyses involves the fact that the distinction between brands and generics is not always clear, both conceptually and empirically. In a number of countries, for example, not only are there "parallel imports" – branded products sold at relatively low prices in some countries, such as southern Europe, and then exported and resold at higher prices to pharmacies in the UK and northern Europe – whose prices are generally in between generic and "domestic" brand prices,[10] but some manufacturers market "branded generics". IMS Health defines branded generics as non-originator products that are either: (i) novel dosage forms of off-patent products, often in combination with another molecule; (ii) on patent with a trade name, but a molecule copy of an originator product; (iii) off-patent with a trade name; or (iv) off-patent without a trade name and from a single source or co-licensed.[11] While in the US in 2009 the branded share of revenue dollars was 76.9%, the branded generic share was 10.6% and the unbranded generic share was 12.5%,[12] in some European countries the branded generic share is considerably larger than in the US.[13] How one classifies parallel imports and branded generics in analyses of brand/generic prices is ambiguous, yet empirical results are likely to be very sensitive to the allocation choice.

The variability across countries in regulatory frameworks, industrial policy, physician/pharmacy autonomy and incentives, brand/generic distinctions, and in how medicine is practiced contributes to making interpretation of cross-country pharmaceutical cost comparisons equivocal. Our goal in this

research is to provide insights into cross-country comparisons by: (i) focusing on a number of therapeutic classes of prescription drugs (11) that between 2004 and 2010 have experienced patent expiration and loss of market exclusivity in eight industrialized countries; (ii) converting revenues and unit sales data to cost per day of treatment and number patient days treated, summed and averaged over all molecules within each therapeutic class regardless of brand/generic status, using the World Health Organizations' Defined Daily Dosage (WHO DDD) metrics; (iii) compare trends across countries and therapeutic classes over time in costs per day of treatment with measures based on price indexes, where the latter is based on the average price per day of treatment for each molecule computed over all versions of the molecule – brands, generics, branded generics and parallel imports – consistent with procedures employed by the US Bureau of Labor Statistics;[14] and (iv) using econometric methods, model and quantify factors affecting variations in price indexes per day of treatment across countries, therapeutic classes and time.

The outline for the remainder of this paper is as follows: In Section II we begin with a description of the underlying IMS MIDAS™ monthly data for eight countries and 11 therapeutic classes, January 2004 through November 2010, and describe the WHO DDD data. Then in Section III we summarize formulae utilized to construct price indexes, and discuss the specification of our various econometric models. In Section IV we first present average cost per day of treatment findings across countries, therapeutic classes and time, and then in Section V we report econometric results at various levels of aggregation, quantifying the impacts on price indexes of daily treatment of generic entry, various national policy changes, pharmacy/physician autonomy, and other factors. In Section VI we report results on expenditures by country and therapeutic class of alternative simulations involving market environment and national policy changes. Finally, in Section VII we provide a summary and interpretation of our principal findings.

II. DATA

Sales data are taken from the IMS Health MIDAS™ database, monthly January 2004-November 2010, covering eight countries: Canada, France, Germany, Italy, Netherlands, Spain, United States (US) and the United Kingdom (UK). For each of these countries, we extract sales data for drugs in 11 Anatomic Therapeutic Chemical (ATC) classes at a mix of the three and four digit ATC, each having notable patent expirations over the 2004-2010 time period: lipid regulators (ATC classes C10A, C10C and C11), antiulcerants (A2B, including both H_2-antagonists and proton pump inhibitors), antidepressants (N6A4, N6A5 and N6A9 – selective serotonin reuptake inhibitors, selective norepinephrine uptake inhibitors, other), antipsychotics (N5A, both typical and atypical), ace inhibitors (C9A and C9B, solo and combination products), calcium channel blockers (C8A and C8B, solo and combination products), osteoporosis (M5B3, M5B9, G3J and H4E), antiplatelets (B1C), beta blockers (C7A and C7B, solo and combination products), non-narcotic analgesics (N2B), and antinauseants (A4A1, serotonin antagonist antiemetic and other). Table 1 reports the ranking of these 11 classes in terms of class retail sales for each of the eight countries in 2005. The 11 ATC classes represent eight of the top 12 retail classes in 2005, comprising the following proportion of total retail prescription drug sales: Canada 46%, France 34%, Germany 30%, Italy 32%, Netherlands 34%, Spain 35%, US 38% and UK 42%. We note in passing that the antinauseants are relatively unimportant in all eight countries and overall, while the non-narcotic analgesics are ranked relatively low except in France and the UK, where they are ranked 10th and 11th largest, respectively. [Place Table 1 somewhere near here]

IMS Health MIDAS™ sales data in local currencies and extended units by form-strength are derived from ex-manufacturer invoices; these data therefore reflect revenues received by manufacturers, they exclude wholesale and retail margins, and therefore do not reflect actual reimbursement by national health authorities or other insurers to the retail sector. The local currency sales were converted to US dollars at constant exchange rates, as of November 2010, for all countries. The MIDAS™ database distinguishes originator brands, parallel imports, and generics (including branded

generics), and over-the-counter (OTC) vs. prescription-only drugs. We transform these sales data into days of therapy utilizing the World Health Organization (WHO) Defined Daily Dosage (DDD) metric. The WHO Collaborating Center for Drug Statistics and Methodology defines the DDD as follows:

> "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults….It should be emphasized that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations….Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use. The DDD provide a fixed unit of measurement independent of price and dosage form (e.g. tablet strength) enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups….*The DDD is nearly always a* ***compromise*** *based on a review of the available information including doses used in various countries when the information is available. The DDD is sometimes a dose that is rarely if ever prescribed, because it is an average of two or more commonly used dose sizes."*[15]

For our purposes, it is useful to note that the WHO DDD assigned to a drug is time invariant, and is identical across countries and dosage strengths. While it would be preferable to utilize the IMS Health daily average consumption (DACON) metric derived and updated from actual retail prescription data, as in Berndt and Aitken [2011], currently IMS Health DACON data are only available for some countries, and not for all those in our sample.

Extended units of a drug are divided by the WHO DDD, thereby converting utilization into days of therapy. Sales of a drug by country converted to US dollars using constant November 2010 exchange rates are then divided by days of therapy to obtain a measure of cost per day of therapy in US dollars. In

our sample of eight countries and 11 therapeutic classes, utilization encompasses over 47 billion DDDs, equivalent to 130 million patient-years. Cost per day of therapy and number of therapy days are computed at both monthly and annual time periods.

Research by IMS Health has involved a comparison of costs of daily treatment based on US DACON data versus that based on WHO DDD data, for seven selected therapeutic classes between 2006 and 2009.[16] A summary of the comparison is presented in Table 2. [Table 2 placed near here]

Several results are striking. First, there is no clear pattern in dollar levels – in five therapeutic classes in all years (antidepressants, antiplatelets, calcium channel blockers, lipid regulators and antiosteoporosis), DACON based daily treatment costs are greater than those based on DDD, whereas in two therapeutic classes (antipsychotics and beta blockers) the reverse occurs. Second, there is no obvious pattern between relative daily costs and relative levels of daily costs across therapeutic areas – DACON based daily costs are less than DDD based costs for both the lowest cost therapeutic class (beta blockers) and for the highest cost therapeutic class (antipsychotics). Third, the proportional differences are not constant. Moreover, there is a clear pattern in differential growth rates. In therapeutic classes where the DACON based daily treatment costs are greater than those based on DDD, the proportional difference grows over time, with 2005 (2009) DACON/WHO DDD ratios being 1.22 (1.30) for antidepressants, 1.22 (1.27) for antiplatelets, 1.41 (1.48) for calcium channel blockers, 1.09 (1.27) for lipid regulators, and 1.00 (1.41) for antiosteoporosis drugs. In comparison, in therapeutic classes where the DACON based daily treatment is less than those based on DDD, the proportional difference also grows over time, with 2005 (2009) ratios being 0.75 (0.68) for antipsychotics, and 0.69 (0.62) for the beta blockers. We conclude that while for data availability reasons we are forced to utilize DDD data, research on differences in DDD vs. DACON based daily cost levels and growth rates merits additional analysis. Given that the DDD values are time and country/region invariant, we will focus more on and give greater credence to results based on growth rates than on levels.

IMS Health compiles regulatory, national health policy, patient copayment, and national/regional reimbursement change events as part of its monitoring in support of the IMS MIDAS™ database product. For each of these events, we assign a +1 if we expect the policy to increase cost per day of therapy, a -1 if we expect it to decrease the cost per day of therapy, and a zero if we expect it to have no impact on cost per day of therapy; we also note the date of the policy event, and designate whether the impact is market wide (across all 11 therapeutic classes), or specific to a given therapeutic class or drug. These policy events are organized separately by country, and by therapeutic class. Appendix A provides details.

Finally, Danzon and Furukawa [2011] have argued persuasively that national health care reimbursement systems can be distinguished based on whether brand-generic decision making is driven largely by pharmacies or by physicians, with the former occurring when patients are incentivized with lower copayments and pharmacies have incentives to purchase the lowest-cost generics available. By contrast, when physicians typically prescribe a specific off-patent molecule by brand name or the originator brand, generic suppliers are incentivized to compete on brand image rather than on price; Danzon and Furukawa characterize such markets as physician driven. Although there are differences among them, Danzon-Furukawa characterize the US, UK , Netherlands and Canadian markets as pharmacy driven and Germany as becoming more so over time, whereas the other European markets in our eight-country sample (France, Italy and Spain) are physician driven. They find costs are generally lower in pharmacy driven markets, other things equal. We adopt the Danzon and Furukawa classification scheme, but in addition characterize France as becoming pharmacy driven in 2006 (when pharmacies were first given strong financial incentives to substitute generics for brands) and Germany in 2007.

III. METHODS

A. Construction of Alternative Price Indexes

We utilize alternative price index formulae to construct price index measures of the cost of a day of treatment in therapeutic class *k* in a country *n* and period *t*. For country *n*, month t, we denote p_{int} as

the cost per day of treatment with drug *i* belonging to class *k*, and q_{int} as the corresponding quantity of treatment days sold. The elementary unit in the various price index calculations is the average price of the molecule over all its marketed drug formulations – brand, generics, branded generics and parallel imports. Specifically, we compute a quantity and price for each molecule *i* and country *n* and period *t*, such that the quantity of molecule *i* in country *n* at *t* is the sum of quantities of drugs *d* sold for that molecule over its various marketed formulations, i.e., $q_{int} = \sum_{d \in i} q_{dnt}$ where q_{dnt} is the quantity of drug formulation *d* and the corresponding price is $p_{int} = \frac{\sum_{d \in i} q_{dnt} p_{dnt}}{q_{int}}$.

Intertemporal fixed weight price indexes employ fixed weights over all time periods, whereas chained price indexes update weights in each time period. We compute the chained Paasche, Laspeyres and Fisher price indices for each therapeutic class k. The chained Laspeyres price index π^l_{knt} uses one period lagged quantity weights, and is defined for class *k*, country *n* and period *t* by:

$$\pi^l_{knt} = \sum_{i \in k} w^l_{int}\, p_{int}$$

where

$$w^l_{int} = \frac{q_{int-1}}{\sum_{j \in k} p_{jnt-1} q_{jnt-1}}.$$

The corresponding chained Paasche price index π^p_{knt} instead uses current period quantity weights, and is defined by:

$$\pi^p_{knt} = \sum_{i \in k} w^p_{int}\, p_{int}$$

where

$$w^p_{int} = \frac{q_{int}}{\sum_{j \in k} p_{jnt-1} q_{jnt}}.$$

For comparison purposes we also construct fixed basis indexes taking the first period of US consumption (January 2004) as the fixed reference time/region. The January 2004 US fixed basis Laspeyres price index is calculated as

$$\pi_{knt}^{l1} = \sum_{i \in k} w_{iUS1}^{l} \, p_{int} \, ,$$

while the January 2004 US fixed basis Paasche price index is constructed as

$$\pi_{knt}^{p1} = \sum_{i \in k} w_{int}^{p1} \, p_{int}$$

where

$$w_{int}^{p1} = \frac{q_{int}}{\sum_{j \in k} p_{jn1} q_{jnt}}.$$

Finally, since the choice between the use of lagged or current quantity weights is somewhat arbitrary, price index researchers frequently employ as a compromise the Fisher Ideal price index π_{knt}^{f} which is defined as the geometric mean of the Paasche and Laspeyres indices:

$$\pi_{knt}^{f} = \sqrt{\pi_{knt}^{p} \pi_{knt}^{l}} \, .$$

Employing these definitions, we normalize the chained price indices to one by country-therapeutic class at the January 2004 initial time period. We note that in our descriptive analyses these normalized price indexes are not comparable in levels across countries or across therapeutic classes. However, they are useful when assessing the evolution over time of price indexes within each therapeutic class and country. We also note that the fixed basis price indexes provide a possible comparison across countries, within a therapeutic class.

B. *Specification of Econometric Models*

We specify various econometric models, at the level of the individual therapeutic class, the individual molecule, and the individual drug. For example, for regressions at the therapeutic class level, we estimate by ordinary least squares (with standard errors clustered at the country-class level) regression equations of the following form, with one observation for therapeutic class *k* for the

therapeutic class level regressions (implicitly constraining coefficients within a therapeutic class and drug formulation to be identical across molecules and drugs):

$$\log \pi_{knt} = \phi_{nk} + \delta_t + \alpha X_{knt} + \varepsilon_{knt} ,$$

where the X_{knt} explanatory variables are defined as follows:

Therapeutic Class Level Explanatory Variables

Time trend	Linear monthly time trend, January 2004 = 1, February 2004 = 2, etc.[17]
ac_price_impact	Index of regulatory events accumulated over time (-1, 0, +1 at each month depending on whether policy event is expected to decrease, have no price impact, or increase price, respectively) at all-country level
ac_price_impact_tcl	Index of regulatory events accumulated over time (-1, 0, +1 at each month depending on whether policy event is expected to decrease, have no price impact, or increase price, respectively) by therapeutic class
expired_cl	Indicator variable equal to one if at least one patent expired in the therapeutic class, else zero
sh_expired	Share of drugs with expired patent within the therapeutic class
sh_expired_pharma	sh_expired interacted with indicator variable equal to one when country generic substitution is pharmacy driven
sh_expired_physic	sh_expired interacted with indicator variable equal to one when country generic substitution is physician driven

The ϕ_{nk} are country-class fixed effect components, capturing the effects of base-country normalized price indexes being set to unity for each country-class in January 2004. Analogous specifications are utilized in the molecule and drug-level regressions. In the context of chained price

indexes, estimates of fixed effects have no ready interpretation. However, when a fixed base period in one country is utilized in constructing the normalized price indexes (e.g., US January 2004 = 1.000 for osteoporosis) that become the dependent variable in the, say, molecule level regressions, the country and class fixed effects parameter estimates are each interpreted as relative to the US January 2004 level for osteoporosis drugs. However, estimated coefficients on the time counter and X_{knt} variables in all the normalized price regressions enable us to infer which regulatory events or other variables affected prices, as well as the magnitude of such effects.

For the most disaggregated regressions at the level of drug formulation, several additional explanatory variables are included in the specification, defined as follows:

Additional Drug Level Explanatory Variables

log_cost	Log price index of cost of daily treatment
expired	Indicator variable equal to one if drug patent has expired (else zero)
off_pat_mth	Number of months since drug patent has expired (else zero)
otc	Indicator variable equal to one if an OTC drug, else zero
generic	Indicator variable equal to one if a generic, else zero

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IV. RESULTS: AVERAGE DAILY COSTS OF THERAPY BY COUNTRY, THERAPEUTIC CLASS AND TIME

Detailed average daily costs of pharmaceutical treatment in US dollars by country, annually by therapeutic class for 2004, 2007 and 2010, based on the WHO DDD metrics are presented in two panels

of Table 3 – the first panel for Canada, France, Germany and Italy, and the second panel for Netherlands, Spain, the UK and the US. The two panels contain a great deal of data, with patterns of results not obvious at first glance.

As an initial step toward uncovering a set of "big picture facts", we have undertaken several unweighted arithmetic mean calculations involving countries and therapeutic areas. To gain a sense of "country level effects", for each country we have calculated the unweighted average of daily cost of therapy over all therapeutic classes for 2004, 2007 and 2010 (taken from Table 3). Inspection of the entries in Table 3 reveals a clear outlier – the antinauseants, which are likely utilized primarily in the inpatient setting, and not via retail, although some retail sales do occur; recall from Table 1 that over all countries, the antinauseants ranked 60th in ex-manufacturer revenues from the retail sector. Several other patterns are evident. The antinauseants, antipsychotics and antiplatelet classes have the highest cost levels in most countries, likely reflecting the fact that they each have several relatively new, patent-protected products. In contrast, the ace inhibitors, beta blockers and calcium channel blockers all contain very old drugs now subject to generic entry, and thus it is not surprising these classes have the lowest daily cost levels. In between are the classes with a mix of old off-patent and new still patent-protected products (antiulcerants, antidepressants, lipid regulators, non-narcotic analgesics, and antiosteoporosis drugs), with daily cost levels in between, reflecting likely the varying vintage composition of the drugs within each therapeutic class.

With these caveats in mind, we first compute annual average costs of daily therapy separately by country but over ten therapeutic classes, excluding antinauseants, as well as over all 11 classes. Results of these summary calculations are presented in Table 4. [Place Table 4 somewhere near here]

Several results are noteworthy. First, comparison of entries in the left panel (ten classes) vs. the right panel (all classes) documents the outlier role played by the antinauseants: in 2004, daily cost levels of therapy including the antinauseants results in daily costs three to four times larger than when they are

excluded, although by 2010 these differences are generally smaller. Second, in 2004, 2007 and 2010, over ten classes, the US and Canada are the highest ranking cost countries, whereas Germany and the UK are lowest cost. However, ranked over all classes including the antinauseants, while the US is highest and Canada second in 2004 and 2007, by 2010 US antinauseant prices have dropped sufficiently more than in Canada (see Table 3), so that Canada becomes the highest cost country, with the US in second place, while Germany remains third highest throughout the 2004-2010 time frame. Germany's shift from lowest cost country when antinauseants are excluded to third highest when they are included is striking. While the UK is second lowest in price throughout the 2004-2010 time period when antinauseants are excluded and remains so in 2004 and 2007 even when antinauseants are included, by 2010 over all classes Germany rises to fifth place.

These very simple level calculations yield interesting observations yet obfuscate many phenomena, including in particular aggregating over diverse therapeutic classes having very different levels and growth rates in daily costs of therapy. An alternative summary of cost of daily treatment trends involves displaying 2004-2010 average annual growth rates (AAGRs) by therapeutic area and by country; we do this in Table 5 below. The "ALL" column is the unweighted average of growth rates in the same row over all eight countries, whereas the bottom two rows of Table 5 are the unweighted mean of the growth rates in each country over all therapeutic classes ("All Classes") and excluding the antinauseants ("Ten Classes"). Since the overwhelming majority of AAGRs are negative, we highlight positive AAGRs in italics. [Place Table 5 somewhere near here]

As seen in Table 5, while most AAGRs are negative, positive AAGRs are clustered in three therapeutic classes – the antipsychotics, non-narcotic analgesics (that in some countries include OTC sales), and antiplatelets; over all eight countries, these AAGRs are 0.88%, -1.10% and -2.67%, respectively. The class with the next lowest decline in daily cost is the beta blockers, whose AAGR over all countries is -4.56%; as seen in Table 3, in numerous countries in 2004 this class of drugs already was

among the lowest daily treatment costs, and thus the room for further cost declines was somewhat limited. Five of the eleven classes experienced double-digit annual declines in daily costs, averaged over all countries: ace inhibitors (-18.92%), the initially very high cost antinauseants (-14.31%), antiulcerants (-12.90%), calcium channel blockers (-12.06%) and lipid regulators (-10.93%), each of which experienced major patent expirations and generic entry. Two other classes having patent expirations experienced slightly smaller but still substantial annual declines in daily treatment costs – antiosteoporosis drugs at -9.31% and antidepressants at -8.17%. Finally, while the antinauseant levels of daily treatment cost are outliers, as discussed above, they also experienced very substantial daily cost declines between 2004 and 2010, and as seen in the bottom right hand corner of Table 5, unweighted AAGRs over all classes at -8.55% are only about half a percentage point greater than when antinauseants are excluded, -7.97%. The only country for which exclusion or inclusion of the antinauseants generates a substantial difference is the US (-9.27% when included, -5.92% when excluded), so in the analysis that follows we focus on results where they are included.

At the bottom of Table 5 we report country-specific AAGRs computed as unweighted averages of growth rates across therapeutic classes. Although there are modest differences among them, the eight countries can be divided into two groups – one group with very substantial daily treatment cost declines (Netherlands with an AAGR of -14.96%, Germany -12.13%, UK -11.56%, and US at -9.27%), and the other group with more modest declines (France -3.72%, Canada -3.84%, Spain -5.29%, Italy -5.65%). Notably, two of the four countries having the smallest declines have been characterized by Danzon-Furukawa [2011] as being physician driven markets (Spain and Italy, and France until 2006), the exception being Canada, whom they identify as being pharmacy-driven, while France became so in 2006. At the other end, Danzon-Furukawa designate three of the four countries having the largest daily cost declines (Netherlands, UK and US) as pharmacy driven, with Germany, the fourth, also becoming more pharmacy-driven in recent years.

As noted earlier, although these various unweighted mean level and AAGR calculations of daily treatment costs are of great interest, they are inadequate in addressing issues of relative utilization, i.e. they do not deal well with differential quantity weighting across therapeutic areas, countries and over time. While economic statisticians attempt and to a considerable degree succeed in addressing differential weighting issues by use of the various price index formulae discussed above, as we shall now see, even with use of state-of-the-art price index formulations, econometric results and their interpretation are still somewhat sensitive to index number formulation and aggregation issues.

V. ECONOMETRIC RESULTS ON INDEXES OF DAILY TREATMENT COSTS

We now move to a discussion of econometric findings utilizing indexes of cost of daily treatment that take into account differential rates of utilization across therapeutic areas, countries and time, based on economic index number formulations. As noted earlier, since there is no clear reason for preferring one time period lagged versus current period weights, we employ the Fisher Ideal weights that are a geometric mean of the one time period lagged (Laspeyres) and current period (Paasche) weights. However, we table econometric results for various Laspeyres and Paasche indexes in Appendix B. [Place Table 6 somewhere near here]

Our initial econometric specification involves use of the Fisher chained indexes where the observations encompass 83 months (January 2004 thru November 2010), 11 therapeutic areas and eight countries (except for Netherlands where data begin in December rather than January 2004, therefore 72 months), and each country and therapeutic has its own chained index, normalized to 1.000 in January 2004; in this first regression, fixed effects are specified as the interaction of country and class. Results from two specifications are presented in Table 6. Estimated standard errors (clustered by country-class) are in parentheses; parameter estimates statistically significant at the 10%, 5% and 1% levels are designated with a *, **, and ***, respectively.

In the first specification, the time trend is significantly negative, while the sh_expired estimate is negative but insignificant. However, when the sh_expired variable is disaggregated into the share of molecules expired in pharmacy vs. physician driven markets (column 2), the estimated coefficient on the sh_expired_pharma variable is negative and statistically significant, whereas the negative estimated coefficient on the sh_expired_physic variable is insignificant, consistent with the notion that pharmacy-driven pharmaceutical markets are more effective at reducing costs than are physician-driven markets; the time counter coefficient estimate is essentially unchanged. In terms of policy impacts, the estimate on the accumulated policy variable is negative and trending toward significance at the country level in both columns (recall that the policy counter assigns policy changes expected to reduce costs with a -1, and policy changes expected to increase costs with a +1 – hence a positive coefficient estimate is consistent with the direction of the hypothesized effect); at the therapeutic class level the estimate is positive but insignificant in both specifications.

Tables B1 and B2 in Appendix B present findings when instead of the chained Fisher, the Laspeyres and Paasche chained price indices are the dependent variable. Estimates on the pharmacy and physician driven variables are similar to those with the Fisher index (negative and significant for sh_expired_pharma, and larger in absolute value that for sh_expired-physic); estimates on the country and therapeutic class accumulated regulatory policy variables are each positive but insignificant for the Laspeyres index, while for the Paasche index the country accumulated regulatory negative estimate becomes statistically significant at the 10% level. Estimates on the time trend term are negative and significant.

The regressions reported in Table 6 have each country's price index for all therapeutic areas set to unity in January 2004. An alternative basing procedure is to have each country's price index in all therapeutic areas be relative to the US price index for that therapeutic area in January 2004, but still retain country*class interacted fixed effects. Results from these alternative specifications for the

Laspeyres, Paasche and Fisher price indexes are presented in Appendix Tables B3, B4 and B5, respectively. The results are qualitatively very similar to those in Appendix Tables B1, B2 and in Table 6 above. In particular, estimates on the pharmacy-driven generic share interaction variable are all negative and significant, and larger in absolute value than that on the physician-generic share interaction variable. Estimates on the monthly time trend are negative and highly significant. Estimates on the accumulated policy change variables are mostly negative at the country level, varying in statistical significance, but positive and insignificant at the therapeutic class level.

A somewhat simpler specification involves using the January 2004 US price index as the reference base, replacing the 88 country*therapeutic class fixed effects with eight country and 11 therapeutic class fixed effects, but otherwise retaining the same set of explanatory variables. In this case estimates on the country indicator variables should be interpreted relative to the US. Estimates with this specification and the Fisher price index are presented in Table 7; estimates utilizing the Laspeyres and Paasche indexes are given in Appendix Tables B6 and B7, respectively. [Place Table 7 near here]

As seen in Table 7, estimates on the time trend coefficient are negative, statistically significant, and considerably larger in absolute value than in Table 6. Estimates on the pharmacy and physician driven share generic variables remain negative, and while both are statistically significant, that on the pharmacy-generic share variable is slightly larger in absolute value. In terms of country fixed effects (all interpreted relative to the US), the estimated coefficient for Canada is positive but insignificant, while that for France is negative and significant at the 10% levele; the increasingly negative estimates for Italy are significant at the 5% level, and the ever larger successively negative estimates for Germany, Spain, Netherlands and the UK are each significant as well, mostly at the 1% level In terms of the accumulated regulatory policy variables, the estimate of the country level impact is negative in both columns, but insignificant in column 2, whereas that at the level of the therapeutic class is positive but insignificant.

The unit of observation underlying the coefficient estimates reported in Tables 6 and 7 is a price index for a given therapeutic class, country and month. It is of course possible to avoid index number issues entirely, and instead estimate models at the level of the individual molecule for each country and month. This greatly increases the number of observation, from about 7,200 to about 200,000. When estimated at this level of molecule detail, we can add several explanatory variables, including whether the patent on that molecule has expired (Generic dummy, and then interacted with pharmacy or physician driven market – Expired*pharmacy driven and Expired*physician driven), months since the molecule has faced generic entry if that occurred during the January 2004 – November 2010 time frame (Off_pat_mth), for those molecules already facing generic entry in January 2004 but whose patent expiration date is unknown (Off_month_unknown), and an indicator variable equal to one if the molecule is sold in an over-the-counter version (OTC dummy).

In Table 8 we report a variety of estimates based on alternative specifications with various explanatory variables included, and several fixed effect specifications. Three alternative regression specifications are estimated each with three alternative fixed effect specifications: With neither molecule nor country*class fixed effects (Columns 1-3), only country*class fixed effects (Columns 4-6), and only molecule across-country fixed effects (Columns 7-9). Although the relevant parameter estimates are quite robust, here we focus our discussion on estimates in Columns 3, 6 and 9. [Place Table 8 somewhere near here]

Monthly time trend estimates are negative for every specification, and significant when molecule fixed effects are included (Column 9). Parameter estimates on the Expired*pharmacy driven variable are negative, significant, and roughly 50-100% larger than the negative estimate on the Expired*physician driven variable. The column 6 and 9 estimates on the Off_month_unknown variable are negative and significant, quite large in absolute value, while estimates on the months off patent counter variable Off_pat_mth are also negative and significant. The coefficient estimate on the OTC

dummy variable is mostly negative, but not statistically significant. Although the estimate on the generic indicator variable is significantly negative in the specification with no molecule or country*class fixed effects (Column 3), it is negative but insignificant when either country*class (Column 6) or molecule (Column 9) fixed effects are included. In terms of the accumulated regulatory policy variables, estimates at the country level are mixed in sign, but positive and insignificant in the molecule and country*class fixed effect specifications (Columns 6 and 9); at the therapeutic class level, the estimates are mostly positive, and of varying statistical significance.

In the specification with no country*class or molecule fixed effects (Column 3), estimates on the therapeutic class indicator variables (interpreted relative to antiosteoporosis drugs) are positive and largest for antinauseants, followed by positive and significant estimates for antipsychotic and antiplatelet drugs, and a positive but insignificant estimate for the non-narcotic analgesic drugs. Estimates on the antiulcerants, lipid regulators, antidepressants, calcium channel blockers, beta blockers and ace inhibitors are all negative and significant, and successively larger in absolute value. Finally, in the same specification with no country*class or molecule fixed effects, estimates on the country indicator variables are interpreted as relative to the US. As seen in column 3, while the estimate for Canada is positive, it is not significant. However, estimates are negative, significant and successively larger in absolute value for the UK, Netherlands, France, Germany, Spain, and Italy, with the latter three being very close to each other in magnitude.

The next set of models estimated are at the level of the specific drug (molecule formulation), where molecules can differ by strength, form, generic vs. brand, and OTC vs. Rx-only. This adds between 75,000 and almost 100,000 observations to the data set. Results are presented in Table 9. As in the previous table, estimates in the first three columns of Table 9 are based on a model without either country*class or molecule fixed effects, those in columns 4-6 have only country*class fixed effects, while those in columns 7-9 have only molecule fixed effects. Again we focus on estimates in columns 3,

6 and 9. Estimates on the monthly time trend variable are positive but insignificant in Columns 3 and 6, but in Column 9 the estimate is negative and significant. Estimates on the expired*pharmacy and expired*physician driven estimates are always negative with the absolute value of the expired*pharmacy being larger than on the expired*physician term, but their statistical significance declines going from columns 3 to 6 to 9. The coefficient estimate on the Off_month_unknown indicator variable is negative, significant and large in absolute value across all models, while the negative estimates on the Off_pat_mth monthly counter variable are similar in magnitude and sign across all models, and are also statistically significant. Estimates of the effect of the specific drug formulation being a generic are uniformly negative and statistically significant. These results imply that once a drug formulation encounters generic competition, other things equal, its price falls substantially immediately and increasingly as time passes. Although the estimates on the OTC indicator variable are consistently negative across all models, they are never significant. In terms of the accumulated regulatory policy variables, across all model specifications, at the country level they are positive, but significant only in Column 9, whereas at the level of the therapeutic class, they are positive and significant in almost all columns, and generally larger than at the country level. [Table 9 somewhere near here]

In the specification with no country*class or molecule fixed effects (Columns 1-3), estimates on the therapeutic class indicator variables are interpreted as relative to the antiosteoporosis drugs. Results in Table 9 are qualitatively very similar to those in Table 8: Daily costs of therapy are highest among the antinauseants, followed by antipsychotics and antiplatelets (the last not statistically significant), followed by the non-narcotic analgesics being of mixed sign relative to antiosteoporosis drugs, but not statistically significant. However, daily costs of therapy are successively smaller than the reference antiosteoporosis drugs in the antiulcerant, lipid regulator and antidepressant classes, and drop even more sharply among the calcium channel blockers, beta blockers and especially the ace inhibitors. Finally, in terms of country fixed effects (all interpreted relative to the US), parameter estimates for

every country are negative (although that for Canada is not significant), and become successively larger in absolute value going from France, to the UK, Netherlands, Italy, Germany and Spain.

One functional form assumption implicit in the regression results reported in Table 9 is that the coefficient on the off patent monthly counter variable is identical across countries. We now explore two alternative models. First, we delete the Off_pat_mth counter variable, and replace it with eight country*Off_pat_mth interaction variables, thereby allowing the effect of time since being off patent to vary across each of the eight countries in our sample. Second, we replace the Off_pat_mth counter variable with two interaction variables, constraining the effect of months off patent to be the same within the four pharmacy driven markets (US, Canada, UK and Netherlands), and the same within the physician driven markets (France until 2006, Germany until 2007, Italy and Spain), but allowing the coefficients on the pharmacy_off interaction variable to differ from that on the physician_off variable. Although this classification is a rough one, we expect it will capture some of the market-wide effects analyzed by Danzon and Furukawa. Results of this estimation are given in Table 10. We focus on results in Columns 2 and 4. [Place Table 10 somewhere near here].

Table 10 shows that once patent expiration occurs, prices fall almost twice as much in pharmacy driven than in physician driven markets; prices also fall further when the molecule formulation is a generic (about 5% of molecules in our sample are off-patent but have no generic competition). According to column 2, while prices increase significantly as months off patent increase in the US, prices decrease but insignificantly as months off patent increase in Italy and Canada, and decrease significantly and at successively greater rates in the Netherlands, France and the UK as months off patent increase. Note that even for the US, the net effect of being off-patent but having no generic competition is negative for the first 82 months after patent expiration (-0.508/0.00616 = 82.5), and is negative for the first 144 months if in addition to being off-patent the molecule faces generic competition (-

0.890/0.00616 = 144.5 Interestingly, as seen in column 4, while the time invariant impact of being off patent is negative and twice as large in pharmacy driven than physician driven markets, the rate of price decline as months off patent increases is larger in physician driven than in pharmacy driven markets. Finally, note that in both these specifications, cumulative regulatory changes have positive impacts, with that at the country level being insignificant and that at the therapeutic class level significant.

VI. IMPLICATIONS FOR POLICY

We now consider policy implications of our econometric findings by simulating the effects of various policy changes on class expenditures, and therefore on savings by therapeutic class, had certain counterfactual policies been adopted. Since these policy changes involve altering the values of certain indicator or other variables, we compute savings in absolute expenditures as the difference in predicted prices with and without the counterfactual policies, multiplied by actual quantities. Note that a more complete analysis would involve in addition the impact of the various policy changes on utilization quantities; given that we have data from eight countries in eleven therapeutic classes, the additional required modeling and estimation would be substantial, and therefore we leave that for future research.

There are two sets of policy counterfactuals whose impacts on costs we will quantify: (i) simulation of the case where all country-period markets were pharmacy driven, instead of some of them for varying time periods being physician driven; and (ii) simulating the cost effects if the regulatory and reimbursement changes that actually occurred since 2004 in various countries had not been implemented.

A. Simulation of All Country-Periods Having Pharmacy Driven Market Environment

For the US, UK and Netherlands, there is no difference between actual and counterfactual, since each of these countries was pharmacy driven during the entire study period. Note that since country specific effects and time effects are confounded with the pharmacy or physician driven characteristic, we cannot disentangle the effect of the pharmacy/physician driven market characteristic on the general

level of prices from other macroeconomic and regulatory events. However, because we have been able to show evidence on the differential effect of the pharmacy/physician driven market characteristic on the prices of drugs experiencing patent expiration, we can calculate the amount of savings that could have been realized had a country adopted regulatory rules making its market more pharmacy driven. This limits the savings to effects on the prices of drugs whose patents expire during our period of analysis. For France and Germany, we simulate the price at the drug level that would prevail had those countries always been pharmacy driven since 2004 instead of being pharmacy driven only after 2006 for France and only after 2007 for Germany. For Italy and Spain, the simulations yield cumulative savings estimates from being pharmacy driven during all of 2004-2010 instead of being physician driven over the full time interval. We simulate the price with a change in this market characteristic using specification (9) of Table 9. Once the counterfactual price is obtained by changing only this market characteristic, keeping everything else constant, we compute cumulative savings in US $ using observed quantities and assuming that these quantities would not change. Of course, as the characteristic "pharmacy driven market" has a larger negative impact on prices than "physician driven", for those countries/time periods involving a switch from physician driven to pharmacy driven, positive savings will result. Assuming that quantities would not change even if prices decrease is a strong assumption, for it could be that quantities would increase and thus that savings would not be as large as what we obtain. However, these savings values are a useful benchmark; we present them in Table 11 in cumulative millions of dollars and as a proportion of cumulative total therapeutic class expenditures. [Place Table 11 somewhere near here]

The entries in Table 11 reveal that measured in absolute expenditures saved, in France the largest cumulative 2004-2005 savings would have occurred among antidepressants, followed closely by non-narcotic analgesics and anti-ulcerants; as a proportion of French therapeutic class expenditures, however, savings are largest for beta blockers, followed by non-narcotic analgesics and then antidepressants. Altogether, in France the cumulative 2004-2005 savings had it been pharmacy rather

than physician driven 2004-2005 would have been about 119 million US$, at 0.84% less than one percent. In the case of Germany, had it been pharmacy driven before 2007 cumulative 2004-2006 absolute magnitudes savings would have been largest for anti-ulcerants and lipid regulators, followed by the beta blockers and then ace inhibitors, in each case greater than 30 million US$; as a proportion of total class expenditures, savings would have been largest among the ace inhibitors and beta blockers, in each case being greater than two percent, whereas savings would have been greater than one percent among the calcium channel blockers, antidepressants, non-narcotics analgesics, lipid regulators, and antiulcerants. Over all classes, total cumulative 2004-2006 savings for Germany would have been about 1.3%. For Italy, which has been physician driven for all seven years between 2004 and 2010, cumulative savings would have been much larger; in absolute expenditures, cumulative savings would have been largest for anti-ulcerants and antiplatelets, about 50 million US$ each, with proportional savings largest for antiplatelets (2.0%) and beta blockers (1.3%); over all 11 therapeutic classes, cumulative savings in Italy would have been more than 250 million US$, slightly less than 1% of total expenditures in these classes over the seven year time period. Finally, for Spain, which was also physician driven for all years 2004-2010, in absolute cumulative expenditures saved, amounts saved would have been largest among the antidepressants, anti-ulcerants and lipid regulators, in each case amounting to more than 50 million US$; as a proportion of total therapeutic class expenditures, cumulative savings would have been greatest for non-narcotic analgesics (2.1%), with savings among beta blockers, ace inhibitors, calcium channel blockers, antidepressants and anti-ulcerants each being between 1.5% and 2.0%. Over all 11 therapeutic classes, cumulative savings in Italy would have been about 367 million US$, constituting about 1.3% of total expenditures in these classes between 2004 and 2010.

These savings may seem relatively modest. Because we have country fixed effects, the simulations capture the savings only from being pharmacy rather than physician driven for those drugs losing patent protection over the 2004-2010 time period. As seen in Table 9, column 9, while the

coefficient estimates on the expired*pharmacy driven and expired*physician driven interaction variables are both negative, the difference between them is rather small (-0.0879 for pharmacy driven and -0.0638 for physician driven, a difference of only -0.0241 – about 2.4 percentage points).

B. Simulation of Expenditures Had No Regulatory Changes Occurred since 2004

Since the US and UK did not introduce any new price-related regulatory or reimbursement policy changes during 2004-2010, there is no relevant counterfactual simulation to be done for these countries. For the other countries, we can simulate the counterfactual prices again using parameter estimates in column (9) of Table 9, setting the class and country cumulative regulatory variables equal to zero for all country-time observations; actual values of these cumulative regulatory variables range from -7 to 2. Here the counterfactual situation is interpreted as not implementing any of the regulatory changes actually implemented during 2004-2010. Again, using the simulated prices, we compute the value of cumulative savings due to the change of regulation using the observed quantities, under the assumption that quantities would have been the same. [Place Tables 12a and 12b somewhere near here]

In Tables 12a and 12b, we present the value of these cumulative savings had price-related regulatory and reimbursement changes not taken place. In all countries except Canada, we find that because expenditures would have been higher without the regulations, the savings from these regulatory policies are positive; in Canada, however, regulatory changes increased expenditures overall by 0.8 percent, with the absolute cumulative expenditures for lipid regulators being just over $100 US million. For countries like France and Germany the cumulative expenditure impacts of regulatory changes are very substantial, much greater than the effect from being pharmacy rather than physician driven. For France, policy changes generated cumulative savings of 1.4 $US billion among the lipid regulators, and almost 1.2 $US billion for antiulcerants. As a proportion of cumulative expenditures, in each therapeutic class cumulative savings were between 12% and 14%. Over the 11 therapeutic classes

selected, French policy changes resulted in cumulative savings of about 6.1 $US billion, on average about 878 $US million annually.

Regulatory and reimbursement policies implemented in Germany 2004-2010 also resulted in substantial cumulative savings, averaging about 14% of total expenditures among the eleven therapeutic classes. Absolute cumulative savings were largest among the anti-ulcerants at 1.1 $US billion, followed by the lipid regulators, antidepressants, antipsychotics and antiplatelets, each over 600 $US million. Over all therapeutic classes, German price-related regulatory and reimbursement policy changes resulted in cumulative savings of almost 5.1 $US billion, on average about 725 $US million annually.

Although still substantial at almost 3 $US billion (415 $US million annually), total cumulative savings in the eleven therapeutic classes from regulatory changes implemented in Italy 2004-2010 were considerably smaller than in France and Germany, and averaged about 10% over the eleven therapeutic classes; the two classes experiencing the greatest cumulative savings were lipid regulators and anti-ulcerants.

Regulatory policy changes implemented in Spain 2004-2010 resulted in more modest cumulative savings, both on an absolute basis (a total of about 1.3 $US billion, or 185 $US million annually) and proportional basis (between 4-5%), and were largest among the lipid regulators and antidepressants. Over the six countries in our sample implementing regulatory policies affecting prices 2004-2010, cumulative savings from these policies were smallest in the Netherlands, totaling 129 $US million over the seven year time period, and reducing expenditures among the eleven therapeutic classes by about 2%.

We conclude, therefore, that various price-related regulatory and reimbursement policies implemented 2004-2010 resulted in quite substantial cumulative savings in France, Germany and Italy. In Spain and especially in the Netherlands the cumulative savings, while positive, were quite small; notably, policy changes implemented in Canada actually increased expenditures. Transitioning from

physician driven to pharmacy driven markets would also have resulted in savings, though for most countries the cumulative amounts saved would have been considerably smaller than cumulative savings attributable to implementing various price-related regulatory and reimbursement policies.

VII. SUMMARY AND CONCLUSIONS

Our goal in this research has been to provide insights into cross-country pharmaceutical cost comparisons by focusing on eleven therapeutic classes that between 2004 and 2010 experienced patent expiration and loss of market exclusivity in eight industrialized countries. Average cost per day of treatment is computed over all versions of the molecule – brands, generics and branded generics – and is measured using the World Health Organization's Defined Daily Dosage metrics. Utilizing index number procedures consistent with the U.S. Bureau of Labor Statistics practices (treating brands and generic versions of the same molecule as perfect substitutes), we have calculated various price indexes. We have also estimated econometric models at various levels of aggregation, quantifying the impacts on price indexes of daily treatment of generic entry, various national price-related regulatory and reimbursement policy changes, pharmacy/physician autonomy, and other factors, and then simulated the effects of alternative market environments and policy changes on expenditures by country/class.

Among our eleven therapeutic classes, unweighted average costs of daily therapy by country differ considerably depending on whether the relatively low volume antinauseants are included. In 2004, 2007 and 2010, over ten classes (excluding antinauseants), the US and Canada are the highest average cost of daily therapy countries, whereas Germany and the UK are lowest; when antinauseants are included, Canada becomes the highest and Germany the third highest cost country. An alternative summary of cost of daily treatment trends involves AAGRs (average annual growth rates) by therapeutic area and country. Over the 2004-2010 time period, while most AAGRs are negative (reflecting in part the impacts of brands losing market exclusivity), positive AAGRs are clustered in three therapeutic classes – antipsychotics, non-narcotic analgesics (that in some countries include OTC products) and

antiplatelets. Five of the eleven classes experienced double-digit declines in daily costs, averaged over all countries: ace inhibitors (-19%), the initially very high cost antinauseants (-14%), anti-ulcerants (-13%), calcium channel blockers (-12%) and lipid regulators (-11%), each of which experienced major patent expirations and generic entry. When country-specific AAGRs are computed as unweighted averages of growth rates across therapeutic classes, the eight countries can be divided into two groups – one with very substantial daily treatment cost declines (Netherlands -15%, Germany -12%, UK -12% and US -9%), and the other group with more modest declines (France -4%, Canada -4%, Spain -5% and Italy -6%). It is worth noting, however, that these cross-country cost comparisons are based on using November 2010 exchange rates; in 2004, 2007 and 2010, foreign currency units per US $ fell for Canada from 1.302 to 1.073 and 1.030, respectively; for the Euro it rose from 1.244 to 1.371 and then fell to 1.324; and for the British pound it initially increased from 1.833 to 2.002 and then fell to 1.544. Hence Canadian and UK costs in US dollars were inflated by exchange rate developments, whereas for the EU countries costs were deflated by exchange rate trends. These cross-country levels and AAGRs are therefore quite sensitive to weighting convention and exchange rate developments.

Econometric findings utilizing price indexes taking into account differential rates of utilization across therapeutic areas, countries and time based on chained Fisher price indexes generally reveal that following loss of patent protection, prices declines are larger in pharmacy than in physician driven markets; estimates on a time trend counter are typically negative and statistically significant as well. Index number issues can be avoided entirely by estimating models at the level of the individual molecule for each country and month. When this is done, thereby greatly increasing the number of observations, we again find that monthly time trend estimates are negative and significant, while negative significant estimates on the expired*pharmacy driven variable are 50-100% larger in absolute value than on the expired*physician driven variable. Unlike in the initial more aggregated models, when estimated at the

level of the individual molecule, coefficient estimates on the cumulative country and therapeutic class price impact variables have the expected sign, although typically they are not statistically significant.

When estimation occurs at an even lower level of aggregation – at the level of molecule formulation (e.g., strength, form, generic vs. brand, and OTC vs. Rx-only) with molecule fixed effects, estimates on the monthly time trend are negative and significant, and the negative estimate on the expired*pharmacy variable is larger than the negative estimate on the expired*physician variable, with only the former being statistically significant. Moreover, parameter estimates imply that once a drug formulation encounters generic competition, other things equal, its price falls substantially immediately and increasingly as time passes. In terms of the accumulated regulatory policy variables, in the fixed molecule effect specification the positive and significant coefficient at the therapeutic class level is greater than the positive estimate at the country level.

Simulations in which in all countries over all time periods have markets being pharmacy rather than physician driven result in cumulative savings ranging from 0.84% and 0.86% in France and Italy, to 1.33-1.34% in Germany and Spain. In interpreting these simulation results, it is worth noting that the model on which they are based includes country and molecule fixed effects, and therefore the only savings realized are those from a molecule going off patent during the 2004-2010 time period. Moreover, since the price data are based on ex-manufacturer invoices, they do not include possible differing wholesale and retail margins in pharmacy vs. physician driven markets. In terms of the cumulative regulatory policy variables, in all countries except Canada price-related regulatory and reimbursement policy changes during the 2004-2010 time frame resulted in savings (in Canada, a very slight increase in total expenditures in the eleven therapeutic classes, less than 1%), savings substantially larger than those were all markets pharmacy rather than physician driven between 2004-2010. The cumulative savings from these price-related regulatory and reimbursement policy changes range from 129 $US million (1.8% of total) in the Netherlands, 1.3 $US billion (4.7% of total) in Spain and 2.9 $US

billion (10.0%) in Italy, to a very substantial 5.1 $US billion (14% of total) in Germany and 6.1 $US billion (13% of total) in France; no major regulatory policy changes were implemented in the UK and the US during this time period. In interpreting the Canadian and EU country savings, it is worth noting that between 2004 and 2010, the Canadian dollar strengthened by about 26% relative to the US dollar, whereas the Euro fell by about 6%.

Finally, while this research presents clear evidence on the downward evolution of prices and thus countries' drug expenditures for therapeutic classes experiencing patent expiration over the 2004-2010 time period, further research needs to be done to assess how this evolution of costs has affected utilization if in any way. Such future research will contribute to understanding which regulatory, reimbursement and market policies are more cost-effective in limiting expenditures without penalizing health care quality.

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Table 1

Class Retail Sales ($US) Rankings among all therapy areas (2005)

Class	Canada	France	Germany	Italy	Netherlands	Spain	UK	US	All Markets
Lipid Regulators	1	1	2	2	1	1	1	1	1
Anti-Ulcerants	2	2	1	1	2	5	3	3	2
Antidepressants	3	5	11	7	5	2	4	2	3
Antipsychotics	7	11	7	21	9	6	7	4	5
Ace Inhibitors	4	6	6	3	7	13	10	16	8
Calcium Channel Blockers	5	9	17	6	13	9	5	11	9
Osteoporosis	10	15	25	19	18	7	15	13	11
Antiplatelets	15	7	13	23	22	11	12	18	12
Beta Blockers	16	13	10	16	12	37	18	21	17
Non-Narcotic Analgesics	66	10	19	35	55	14	11	61	35
Antinauseants	65	74	78	79	63	97	90	43	60

Table 2

COMPARISON OF US DAILY COST OF THERAPY BY THERAPEUTIC CLASS, 2006-2009
BASED ON IMS HEALTH DACON AND WORLD HEALTH ORGANIZATION DDD MEASURES

	Dollar Daily Cost IMS DACON				Dollar Daily Cost WHO DDD				DACON/DDD RATIO	
Class	2006	2007	2008	2009	2006	2007	2008	2009	2006	2009
Antidepressants	$1.63	$1.43	$1.41	$1.31	$1.31	$1.14	$1.11	$1.01	1.22	1.30
Antiplatelets	3.30	3.37	3.82	4.20	2.71	2.77	3.04	3.30	1.22	1.27
Antipsychotics	6.72	7.18	7.68	7.42	8.98	9.67	10.45	10.89	0.75	0.68
Beta Blockers	0.67	0.59	0.27	0.30	0.97	0.82	0.39	0.48	0.69	0.62
Calcium Channel Blockers	1.24	0.86	0.52	0.43	0.88	0.61	0.35	0.29	1.41	1.48
Lipid Regulators	2.41	1.94	1.77	1.70	2.21	1.73	1.46	1.34	1.09	1.27
Antiosteoporosis	2.24	2.34	2.16	2.10	2.25	2.38	1.75	1.49	1.00	1.41

Table 3

Average Daily Cost of Treatment, by Country, Therapeutic Class, and Selected Years, in Dollars

	CANADA			FRANCE		
Therapeutic Class	2004	2007	2010	2004	2007	2010
Ace Inhibitors	0.4323	0.3363	0.2788	0.5191	0.4034	0.3103
Antiulcerants	1.6050	1.4750	1.0863	1.5294	1.1360	0.7750
Antidepressants	1.0237	0.9111	0.8923	0.7555	0.6129	0.5627
Antinauseants	38.3146	28.2146	25.0065	20.3702	16.8510	9.9183
Antiplatelets	2.1588	1.9199	2.2017	2.1810	2.0816	1.1806
Antipsychotics	5.0407	4.9649	3.7782	2.5055	2.7305	2.7153
Beta Blockers	0.4945	0.4785	0.4398	0.3311	0.3295	0.3079
Calcium Channel Blockers	1.0215	1.0220	0.6952	0.5252	0.4338	0.3068
Lipid Regulators	1.7327	1.5650	1.1958	1.0123	0.7688	0.7255
Non-Narcotic Analgesics	0.3427	0.4051	0.4245	0.5475	0.5137	0.4986
Antiosteoporosis	1.3205	1.1157	0.9792	1.3221	1.0593	0.9697

	GERMANY			ITALY		
Therapeutic Class	2004	2007	2010	2004	2007	2010
Ace Inhibitors	0.1833	0.0491	0.0240	0.3673	0.2671	0.1458
Antiulcerants	1.2072	0.6848	0.3973	1.3930	0.9131	0.6111
Antidepressants	0.7994	0.6116	0.4664	0.7649	0.5827	0.5162
Antinauseants	32.8597	24.4701	18.5439	21.1108	19.1345	12.7710
Antiplatelets	1.3156	1.2266	1.1185	0.9911	1.0727	1.0715
Antipsychotics	1.9982	2.2722	1.8765	2.9207	3.0644	3.2539
Beta Blockers	0.3331	0.2374	0.1324	0.3226	0.2984	0.2856
Calcium Channel Blockers	0.2894	0.1167	0.0762	0.4270	0.3885	0.2677
Lipid Regulators	1.0316	0.4379	0.2768	1.3307	0.9721	0.7361
Non-Narcotic Analgesics	0.5912	0.5545	0.5109	1.0948	1.0581	1.1146
Antiosteoporosis	1.4796	1.1223	0.7754	1.2063	0.8636	0.8755

Table 3 (Continued)

Average Daily Cost of Treatment, by Country, Therapeutic Area, and Selected Years, in Dollars

	NETHERLANDS			SPAIN		
Therapeutic Class	2004	2007	2010	2004	2007	2010
Ace Inhibitors	0.3385	0.2733	0.0469	0.1988	0.1360	0.0904
Antiulcerants	1.0015	0.8799	0.2753	0.5378	0.4204	0.3120
Antidepressants	0.7912	0.6464	0.2125	0.7597	0.6859	0.5939
Antinauseants	23.2530	16.6379	3.9232	18.3570	14.6750	11.3698
Antiplatelets	1.8975	1.7040	0.9194	1.4163	1.5028	1.4491
Antipsychotics	3.3376	3.6511	3.3231	3.1692	3.1709	3.0646
Beta Blockers	0.3387	0.3326	0.2018	0.2739	0.2520	0.2373
Calcium Channel Blockers	0.3692	0.3183	0.1709	0.4967	0.4089	0.3308
Lipid Regulators	0.9918	0.8958	0.4579	1.0651	0.8666	0.6269
Non-Narcotic Analgesics	0.6028	0.5056	0.3124	0.4495	0.4229	0.3762
Antiosteoporosis	1.3633	1.0261	0.4279	1.2704	1.0636	0.9331
	UK			**US**		
Therapeutic Class	2004	2007	2010	2004	2007	2010
Ace Inhibitors	0.2662	0.1131	0.0440	0.2236	0.1316	0.0344
Antiulcerants	0.9653	0.3605	0.2101	2.1954	2.0537	1.5149
Antidepressants	0.6664	0.3988	0.2607	1.3754	1.1398	1.0217
Antinauseants	21.9333	18.7966	15.2268	59.0559	28.9133	2.0729
Antiplatelets	1.2311	1.4525	0.9091	2.7247	2.7618	3.7252
Antipsychotics	2.9063	3.5701	3.4187	7.8807	9.6638	12.1482
Beta Blockers	0.1978	0.2122	0.2042	0.7686	0.8372	0.4976
Calcium Channel Blockers	0.4939	0.2356	0.1517	0.8361	0.6021	0.2570
Lipid Regulators	1.1065	0.4503	0.3417	2.2867	1.7361	1.3290
Non-Narcotic Analgesics	0.3404	0.4280	0.3605	0.2594	0.3142	0.3205
Antiosteoporosis	1.1562	0.5711	0.2594	2.0718	2.3769	1.5697

Table 4

Unweighted Mean Daily Cost of Therapy Across Therapeutic Classes, Selected Years

	Over Ten Classes*			Over All Classes*		
	2004	2007	2010	2004	2007	2010
Canada	$1.517	$1.419	$1.197	$4.862	$3.855	$3.362
France	1.123	1.007	0.835	2.873	2.448	1.661
Germany	0.923	0.731	0.565	3.826	2.889	2.200
Italy	1.082	0.948	0.888	2.903	2.601	1.968
Netherlands	1.103	1.023	0.635	3.117	2.443	0.934
Spain	0.964	0.893	0.801	2.545	2.146	1.762
UK	0.933	0.779	0.616	2.842	2.417	1.944
US	2.062	2.162	2.242	7.244	4.594	2.226

*"Ten Classes" excludes the antinauseants, "All Classes" includes them

Table 5

2004-2010 Average Annual Growth Rates by Therapeutic Area, Country, and Overall, in Percent

	CAN	FRA	GER	ITA	NET	SPA	UK	US	ALL
Ace Inhibitors	-7.05	-8.22	-28.74	-14.27	-28.07	-12.31	-25.92	-26.80	-18.92
Antiulcerants	-6.30	-10.71	-16.91	-12.83	-19.36	-8.68	-22.44	-6.00	-12.90
Antidepressants	-2.26	-4.79	-8.59	-6.34	-19.68	-4.02	-14.48	-4.83	-8.17
Antinauseants	-6.86	-8.45	-9.09	-8.04	-25.66	-7.67	-5.90	-42.78	-14.31
Antiplatelets	*0.30*	-9.72	-2.67	*1.31*	-11.38	*0.38*	-4.93	*5.35*	-2.67
Antipsychotics	-4.69	*1.35*	-1.04	*1.82*	-0.07	-0.56	*2.74*	*7.48*	*0.88*
Beta Blockers	-1.93	-1.20	-14.25	-2.01	-8.27	-2.36	*0.53*	-6.99	-4.56
Calcium Channel Blockers	-6.21	-8.57	-19.94	-7.49	-12.05	-6.55	-17.86	-17.85	-12.06
Lipid Regulators	-6.00	-5.40	-19.69	-9.40	-12.09	-8.45	-17.79	-8.65	-10.93
Non-narcotic Analgesics	*3.63*	-1.55	-2.40	*0.30*	-10.38	-2.92	*0.96*	*3.59*	-1.10
Antiosteoporosis	-4.86	-5.04	-10.21	-5.20	-17.56	-5.01	-22.05	-4.52	-9.31
Mean Growth Rates:									
All Classes	-3.84	-3.72	-12.13	-5.65	-14.96	-5.29	-11.56	-9.27	-8.55
Ten Classes*	-3.54	-3.24	-12.44	-5.41	-13.83	-5.05	-12.12	-5.92	-7.97

*"Ten Classes" excludes the antinauseants

Table 6: Regressions with Fisher Chained Indices

Therapeutic Class Level of Aggregation, Country*-Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.000567***	-0.000559***
	(0.000148)	(0.000148)
sh_expired	-0.0259	
	(0.0171)	
sh_expired_pharma		-0.0330*
		(0.0193)
sh_expired_physic		-0.0188
		(0.0173)
Regulatory Changes		
ac_price_impact	-0.00768*	-0.00693*
	(0.00401)	(0.00408)
ac_price_impact_tcl	0.00369	0.00210
	(0.00238)	(0.00278)
Constant	0.0211**	0.0215**
	(0.00851)	(0.00840)
Observations	7,095	7,095
R-squared	0.028	0.029
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table 7: Regressions with Fisher (fixed US January 2004 = 1.000 basis) Indices
Fixed Effects by Country and Class, not Country*Class
Therapeutic Class Level of Aggregation

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.01000***	-0.00997***
	(0.00176)	(0.00176)
sh_expired	-0.937***	
	(0.137)	
sh_expired_pharma		-0.981***
		(0.208)
sh_expired_physic		-0.865***
		(0.0982)
Regulatory Changes		
ac_price_impact	-0.0464*	-0.0399
	(0.0214)	(0.0246)
ac_price_impact_tcl	0.0197	0.00675
	(0.0135)	(0.0281)
Country Dummies (reference is US)		
CANADA	0.0121	0.0107
	(0.161)	(0.160)
FRANCE	-0.286	-0.326*
	(0.169)	(0.175)
GERMANY	-0.549**	-0.622*
	(0.207)	(0.280)
ITALY	-0.495**	-0.566**
	(0.221)	(0.252)
NETHERLANDS	-0.642***	-0.640***
	(0.194)	(0.196)
SPAIN	-0.727***	-0.790***
	(0.196)	(0.201)
UK	-0.770***	-0.767***
	(0.203)	(0.204)
Constant	0.404**	0.432*
	(0.180)	(0.197)
Observations	7,183	7,183
R-squared	0.502	0.503
Class FE	Yes	Yes

Standard errors clustered by country-class

Table 8: Results from Estimation with Observations at the Molecule Level

VARIABLES	(1) $log\pi_{int}$	(2) $log\pi_{int}$	(3) $log\pi_{int}$	(4) $log\pi_{int}$	(5) $log\pi_{int}$	(6) $log\pi_{int}$	(7) $log\pi_{int}$	(8) $log\pi_{int}$	(9) $log\pi_{int}$
Time trend (monthly)	-0.000169	-0.000288	-0.000272	-0.000301	-0.000179	-0.000169	-0.00244***	-0.00204***	-0.00200***
	(0.000866)	(0.000877)	(0.000859)	(0.000891)	(0.000879)	(0.000857)	(0.000790)	(0.000770)	(0.000761)
Expired	-0.744***	-0.853***		-0.787***	-0.668***		-0.455***	-0.363***	
	(0.155)	(0.121)		(0.120)	(0.154)		(0.0613)	(0.0653)	
Expired*pharmacy driven			-0.962***			-0.787***			-0.444***
			(0.129)			(0.162)			(0.0726)
Expired*physician driven			-0.658***			-0.463***			-0.254***
			(0.128)			(0.151)			(0.0615)
Off_pat_mth	-0.00109*				-0.00117*	-0.00111		-0.00173***	-0.00167***
	(0.000654)				(0.000688)	(0.000686)		(0.000537)	(0.000535)
Off_month_unknown	-0.361*				-0.466**	-0.498**		-0.379**	-0.399**
	(0.201)				(0.188)	(0.192)		(0.156)	(0.155)
OTC dummy	-0.0609	-0.0641	-0.0580	0.0170	0.0204	0.0245	-0.0871	-0.102	-0.0919
	(0.151)	(0.151)	(0.150)	(0.143)	(0.139)	(0.137)	(0.324)	(0.310)	(0.306)
Generic dummy	-0.248	-0.486***	-0.471***	-0.570***	-0.237	-0.189	-0.290***	-0.0948	-0.0601
	(0.193)	(0.113)	(0.111)	(0.115)	(0.191)	(0.191)	(0.0876)	(0.139)	(0.138)
Regulatory Changes									
ac_price_impact	-0.0147	-0.0168	-0.00207	-0.0163	-0.0140	0.00221	-0.00513	-0.00443	0.00451
	(0.0153)	(0.0154)	(0.0166)	(0.0147)	(0.0145)	(0.0156)	(0.00711)	(0.00705)	(0.00654)
ac_price_impact_tcl	0.0353**	0.0352**	-0.00416	0.0366**	0.0366**	-0.00534	0.0324***	0.0321***	0.00756
	(0.0154)	(0.0155)	(0.0176)	(0.0157)	(0.0156)	(0.0175)	(0.00661)	(0.00658)	(0.00937)
Therapeutic Classes Dummies (Reference is Osteoporosis)									
Ace Inhibitors	-1.280***	-1.262***	-1.250***						
	(0.147)	(0.148)	(0.146)						
Anti-Ulcerants	-0.270**	-0.271**	-0.266**						
	(0.110)	(0.112)	(0.113)						
Antidepressants	-0.350***	-0.373***	-0.365***						
	(0.103)	(0.105)	(0.105)						
Antinauseants	2.791***	2.801***	2.814***						
	(0.121)	(0.121)	(0.121)						
Antiplatelets	0.314**	0.285*	0.277*						
	(0.141)	(0.144)	(0.142)						
Antipsychotics	0.512***	0.500***	0.503***						
	(0.128)	(0.126)	(0.127)						
Beta Blockers	-0.579***	-0.625***	-0.617***						
	(0.120)	(0.116)	(0.119)						
Calcium Channel Blockers	-0.603***	-0.614***	-0.605***						
	(0.130)	(0.132)	(0.133)						
Lipid Regulators	-0.311***	-0.320***	-0.324***						
	(0.110)	(0.112)	(0.111)						
Non-Narcotic_Analgesics	0.0861	0.0515	0.0476						
	(0.154)	(0.152)	(0.149)						

Table 8: Continued

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Country Dummies (Ref is US)									
CANADA	0.122	0.115	0.113				0.145	0.150	0.147
	(0.127)	(0.128)	(0.126)				(0.102)	(0.102)	(0.102)
FRANCE	-0.313**	-0.322**	-0.448***				-0.317***	-0.306***	-0.387***
	(0.146)	(0.142)	(0.148)				(0.112)	(0.110)	(0.0986)
GERMANY	-0.356***	-0.369***	-0.597***				-0.295***	-0.273***	-0.417***
	(0.122)	(0.118)	(0.140)				(0.0911)	(0.0898)	(0.0723)
ITALY	-0.364***	-0.380***	-0.613***				-0.363***	-0.360***	-0.504***
	(0.136)	(0.135)	(0.160)				(0.104)	(0.105)	(0.0808)
NETHERLANDS	-0.410***	-0.397***	-0.396***				-0.398***	-0.410***	-0.410***
	(0.117)	(0.115)	(0.114)				(0.0989)	(0.0980)	(0.0979)
SPAIN	-0.373***	-0.393***	-0.604***				-0.456***	-0.431***	-0.561***
	(0.117)	(0.115)	(0.148)				(0.109)	(0.109)	(0.0871)
UK	-0.382***	-0.399***	-0.393***				-0.427***	-0.398***	-0.395***
	(0.116)	(0.112)	(0.110)				(0.0900)	(0.0885)	(0.0887)
Constant	1.064***	1.084***	1.152***	0.574***	0.579***	0.559***	0.547***	0.586***	0.636***
	(0.127)	(0.123)	(0.126)	(0.0737)	(0.0730)	(0.0684)	(0.0838)	(0.0864)	(0.0804)
Observations	205,113	205,113	205,113	205,113	205,113	205,113	205,113	205,113	205,113
R-squared	0.501	0.499	0.502	0.219	0.225	0.230	0.149	0.158	0.161
Molecule Fixed Effect	No	No	No	No	No	No	Yes	Yes	Yes
Country-Class Fixed Effect	No	No	No	Yes	Yes	Yes	No	No	No

Table 9: Results from Estimation with Observations at the Specific Molecule Formulation (Drug) Level

VARIABLES	(1) $logp_{int}$	(2) $logp_{int}$	(3) $logp_{int}$	(4) $logp_{int}$	(5) $logp_{int}$	(6) $logp_{int}$	(7) $logp_{int}$	(8) $logp_{int}$	(9) $logp_{int}$
Time trend (monthly)	0.000462	0.000354	0.000356	0.000300	0.000397	0.000400	-0.00155**	-0.00129**	-0.00129**
	(0.000771)	(0.000789)	(0.000786)	(0.000787)	(0.000767)	(0.000763)	(0.000613)	(0.000591)	(0.000590)
Expired	-0.452***	-0.533***		-0.488***	-0.412***		-0.132***	-0.0797*	
	(0.131)	(0.113)		(0.115)	(0.132)		(0.0376)	(0.0414)	
Expired*pharmacy driven			-0.572***			-0.458***			-0.0879*
			(0.123)			(0.143)			(0.0460)
Expired*physician driven			-0.449***			-0.316**			-0.0638
			(0.115)			(0.126)			(0.0421)
Off_pat_mth	-0.000968**				-0.000917**	-0.000908**		-0.00105***	-0.00105***
	(0.000441)				(0.000453)	(0.000454)		(0.000357)	(0.000357)
Off_month_unknown	-0.371***				-0.412***	-0.412***		-0.305***	-0.305***
	(0.136)				(0.104)	(0.105)		(0.0726)	(0.0727)
OTC dummy	-0.146	-0.151	-0.148	-0.0662	-0.0607	-0.0587	-0.0785	-0.0876	-0.0870
	(0.172)	(0.170)	(0.170)	(0.147)	(0.149)	(0.148)	(0.212)	(0.212)	(0.212)
Generic dummy	-0.437***	-0.704***	-0.703***	-0.736***	-0.423***	-0.421***	-0.673***	-0.476***	-0.476***
	(0.123)	(0.106)	(0.106)	(0.107)	(0.0971)	(0.0988)	(0.0409)	(0.0710)	(0.0711)
ac_price_impact	0.0144	0.0138	0.0197	0.0133	0.0139	0.0209	0.0235***	0.0231***	0.0243***
	(0.0141)	(0.0144)	(0.0159)	(0.0134)	(0.0130)	(0.0145)	(0.00584)	(0.00585)	(0.00603)
ac_price_impact_tcl	0.0447***	0.0448***	0.0278	0.0468***	0.0465***	0.0268*	0.0429***	0.0426***	0.0393***
	(0.0162)	(0.0165)	(0.0168)	(0.0162)	(0.0160)	(0.0161)	(0.00666)	(0.00660)	(0.00839)
<u>Therapeutic Classes Dummies</u> (Reference is Osteoporosis)									
Ace Inhibitors	-1.259***	-1.247***	-1.245***						
	(0.153)	(0.155)	(0.156)						
Anti-Ulcerants	-0.244*	-0.249*	-0.248*						
	(0.134)	(0.137)	(0.138)						
Antidepressants	-0.335***	-0.358***	-0.357***						
	(0.122)	(0.124)	(0.125)						
Antinauseants	2.800***	2.807***	2.810***						
	(0.144)	(0.144)	(0.145)						
Antiplatelets	0.249	0.222	0.219						
	(0.158)	(0.161)	(0.161)						
Antipsychotics	0.473***	0.461***	0.461***						
	(0.137)	(0.137)	(0.139)						
Beta Blockers	-0.637***	-0.689***	-0.688***						
	(0.134)	(0.138)	(0.140)						
Calcium Channel Blockers	-0.662***	-0.683***	-0.682***						
	(0.134)	(0.137)	(0.138)						
Lipid Regulators	-0.263**	-0.265**	-0.267**						
	(0.120)	(0.121)	(0.122)						
Non-Narcotic Analgesics	0.0144	-0.00807	-0.00997						
	(0.182)	(0.184)	(0.184)						

Table 9 continued

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Country Dummies (Reference is US)									
CANADA	-0.128	-0.130	-0.131				-0.0947	-0.0940	-0.0944
	(0.105)	(0.107)	(0.106)				(0.0837)	(0.0835)	(0.0833)
FRANCE	-0.595***	-0.605***	-0.662***				-0.600***	-0.591***	-0.603***
	(0.136)	(0.135)	(0.136)				(0.102)	(0.101)	(0.0924)
GERMANY	-0.686***	-0.689***	-0.789***				-0.607***	-0.598***	-0.618***
	(0.105)	(0.103)	(0.117)				(0.0785)	(0.0776)	(0.0644)
ITALY	-0.670***	-0.666***	-0.770***				-0.666***	-0.673***	-0.694***
	(0.125)	(0.124)	(0.143)				(0.0938)	(0.0945)	(0.0748)
NETHERLANDS	-0.780***	-0.760***	-0.761***				-0.737***	-0.750***	-0.750***
	(0.103)	(0.103)	(0.103)				(0.0875)	(0.0868)	(0.0866)
SPAIN	-0.720***	-0.715***	-0.808***				-0.806***	-0.803***	-0.821***
	(0.104)	(0.104)	(0.127)				(0.0959)	(0.0964)	(0.0795)
UK	-0.691***	-0.711***	-0.709***				-0.719***	-0.698***	-0.697***
	(0.0954)	(0.0927)	(0.0927)				(0.0795)	(0.0785)	(0.0787)
Constant	1.304***	1.319***	1.349***	0.489***	0.492***	0.482***	0.734***	0.757***	0.763***
	(0.140)	(0.138)	(0.142)	(0.0696)	(0.0688)	(0.0664)	(0.0643)	(0.0641)	(0.0596)
Observations	302,595	302,595	302,595	302,595	302,595	302,595	302,595	302,595	302,595
R-squared	0.505	0.501	0.502	0.227	0.233	0.234	0.280	0.285	0.285
Molecule Fixed Effect	No	No	No	No	No	No	Yes	Yes	Yes
Country-Class Fixed Effect	No	No	No	Yes	Yes	Yes	No	No	No

Standard errors clustered by country-class

Table 10: Results from Estimation with Observations at the Molecule Formulation (Drug) Level

VARIABLES	(1) $logp_{int}$	(2) $logp_{int}$	(3) $logp_{int}$	(4) $logp_{int}$
Time trend (monthly)	0.000324	0.000328	0.000397	0.000402
	(0.000778)	(0.000772)	(0.000768)	(0.000762)
Expired	-0.450***		-0.406***	
	(0.130)		(0.134)	
Expired*pharmacy driven		-0.508***		-0.471***
		(0.140)		(0.142)
Expired*physician driven		-0.327**		-0.264*
		(0.128)		(0.141)
Off month*unknown	-0.414***	-0.415***	-0.415***	-0.417***
	(0.107)	(0.108)	(0.103)	(0.105)
OTC	-0.0630	-0.0601	-0.0601	-0.0569
	(0.142)	(0.141)	(0.149)	(0.148)
generic	-0.384***	-0.382***	-0.423***	-0.421***
	(0.0921)	(0.0940)	(0.0957)	(0.0973)
Interactions country dummy with off				
CANADA*off patent months	-0.000921	-0.000868		
	(0.000673)	(0.000678)		
FRANCE*off patent months	-0.00208**	-0.00207**		
	(0.000819)	(0.000821)		
GERMANY*off patent months	-0.00118**	-0.00118**		
	(0.000531)	(0.000533)		
ITALY*off patent months	-0.000209	-0.000551		
	(0.000738)	(0.000750)		
NETHERLANDS*off patent months	-0.00176**	-0.00171**		
	(0.000766)	(0.000770)		
SPAIN*off patent months	-0.00306**	-0.00323**		
	(0.00130)	(0.00132)		
UK*off patent months	-0.00216***	-0.00212***		
	(0.000653)	(0.000657)		
USA*off patent months	0.00609***	0.00616***		
	(0.00117)	(0.00117)		
Pharmacy*off patent months			-0.000724	-0.000633
			(0.000478)	(0.000490)
Physician*off patent months			-0.00178**	-0.00211***
			(0.000685)	(0.000736)
Regulatory changes				
ac_price_impact	0.0100	0.0187	0.0117	0.0211
	(0.0129)	(0.0145)	(0.0129)	(0.0143)
ac_price_impact_tcl	0.0444***	0.0193	0.0543***	0.0289*
	(0.0158)	(0.0158)	(0.0181)	(0.0166)
Constant	0.497***	0.482***	0.497***	0.484***
	(0.0700)	(0.0670)	(0.0681)	(0.0660)
Observations	302,595	302,595	302,595	302,595
R-squared	0.269	0.271	0.234	0.236
Country-Class Fixed Effect	Yes	Yes	Yes	Yes

Standard errors clustered by country-class

Table 11: Cumulative Savings in Million $ US and as Percent of Total Therapeutic Class Expenditures if Country was a pharmacy driven market during 2004-2010 (for France and Germany, cumulative savings due to changes only before 2006 and 2007, respectively)

Savings	FRANCE (2004-2005)		GERMANY (2004-2006)		ITALY		SPAIN	
Therapeutic Class	Million US $	% Expenses	Million US $	% Expenses	Million US $	% Expenses	Million US $	% Expenses
Ace Inhibitors	3,69	0,38	30,26	2,24	27,22	1,12	17,86	1,94
Anti-Ulcerants	22,19	0,78	39,79	1,10	53,39	0,92	60,21	1,52
Antidepressants	25,70	1,69	27,64	1,55	27,28	1,03	73,28	1,66
Antinauseants	0,00	0,00	0,26	0,47	0,75	0,81	0,79	1,44
Antiplatelets	0,66	0,06	11,76	0,61	49,39	2,01	40,79	1,34
Antipsychotics	4,24	0,62	8,64	0,58	5,22	0,36	14,67	0,50
Beta Blockers	14,89	2,23	34,46	2,01	20,86	1,31	11,37	1,99
Calcium Channel Blockers	8,78	0,89	23,18	1,95	26,60	0,92	32,58	1,81
Lipid Regulators	12,34	0,36	38,29	1,36	18,79	0,32	54,03	0,95
Non-Narcotic Analgesics	22,86	2,00	17,30	1,47	14,20	1,10	43,61	2,11
Osteoporosis	3,55	0,50	6,26	0,95	7,26	0,57	18,28	0,89
Total	118,89	0,84	237,83	1,33	250,95	0,86	367,46	1,34

Table 12a: Cumulative savings (increased expenditure if negative) in Million $ US during 2004-2010 if Country had not changed regulatory policies since 2004

Therapeutic Class	CANADA		FRANCE		GERMANY	
	Million US $	% Expenses	Million US $	% Expenses	Million US $	% Expenses
Ace Inhibitors	-28,40	-0,72	378,66	12,89	212,89	11,06
Antiulcerants	-59,72	-0,82	1158,00	12,86	1131,50	15,35
Antidepressants	-43,11	-0,75	617,96	13,11	640,99	16,28
Antinauseants	-1,11	-0,67	23,58	11,55	25,94	18,07
Antiplatelets	-16,66	-0,66	605,18	13,60	613,39	14,54
Antipsychotics	-22,58	-0,71	385,55	14,54	615,92	16,62
Beta Blockers	-9,90	-0,78	340,62	14,08	422,79	13,87
Calcium Channel Blockers	-41,78	-0,93	405,80	12,84	240,88	12,57
Lipid Regulators	-104,25	-0,89	1425,54	13,30	680,72	13,51
Non-Narcotic Analgesics	-9,45	-0,66	551,40	12,75	303,94	11,29
Osteoporosis	14,32	-0,85	254,87	12,73	183,00	14,47
Total	351,27	-0,81	6147,16	13,19	5071,94	14,38

Table 12b: Cumulative savings (increased expenditure if negative) in Million $ US during 2004-2010 if Country had not changed regulatory policies since 2004

Therapeutic Class	ITALY		NETHERLANDS		SPAIN	
	Million US $	% Expenses	Million US $	% Expenses	Million US $	% Expenses
Ace Inhibitors	274,70	9,51	3,59	0,87	33,72	3,60
Antiulcerants	619,07	10,25	26,88	1,67	185,22	4,69
Antidepressants	263,14	9,91	8,06	1,14	209,62	4,75
Antinauseants	11,90	9,49	0,39	1,04	2,38	4,23
Antiplatelets	271,98	11,07	12,71	2,40	152,53	5,02
Antipsychotics	160,87	11,12	15,19	2,50	137,75	4,84
Beta Blockers	163,70	10,33	10,38	2,11	27,16	4,75
Calcium Channel Blockers	316,78	9,70	6,70	1,70	77,23	4,27
Lipid Regulators	624,19	10,41	39,62	1,90	269,41	4,71
Non-Narcotic Analgesics	66,69	5,15	1,41	2,30	93,81	4,55
Osteoporosis	134,05	10,39	4,36	1,47	100,49	4,79
Total	2907,05	10,01	129,28	1,79	1289,31	4,69

Appendix A:

Regulatory, Reimbursement, Patient Copayment, and Related Policy Event Data

Information on regulatory change events is coded qualitatively to evaluate whether they have an impact on prices and whether the impact is of the expected sign. Data are taken from the IMS Health MIDAS™ database product.

Country	Impact	Date	Expected Price Impact on Global Market (-1,0,+1)
Canada	Maximum list price of new generics set at 42% and existing generics at 50% of originator drug in British Columbia	oct-10	-1
Canada	Ontario cuts generic prices by 25%	apr-10	-1
Canada	Maximum list price of new generics at 45% and existing generics at 56% of originator drug in Alberta	febr-10	-1
Canada	Quebec lifts price freeze for first time in 13 years over concern that products will be removed from the provincial formulary if price increases are not permitted	jan-07	+1
France	Cost containment measures put in place by Commission: Delisting of drugs currently reimbursed at 35% to 15%; fixed co-payment for chronic disease patients; annual deductible for healthcare costs	august-10	0
France	Parallel import price cuts of 5% off manufacturer's selling price	june-10	-1
France	Generic Price Cuts: New generics must be priced at 55% (up from 50%) below MSP; after being on the market for 18 months these new generics will be cut 7% (up from 4%) and the off-patent original by 12.5% (up from 10%)	sept-08	-1
France	Non-reimbursed drug prices agreement signed: manufacturers must set the prices at a level which will ensure all patients may access them and pharmacists must	apr-08	0

	ensure prices prices are transparent		
France	206 off-patent branded products and generics experience price cuts ranging from 4-15% off the ex-manufacturer selling price	febr-08	-1
France	Price increase for veintonics - almost doubled as a result of being delisted -VAT is roughly 3.4% higher for nonreimbursed drugs	jan-08	+1
France	Therapeutic off-patent price referencing to cut patented drug prices	oct-06	0
France	Drugs delisted in March 2006 haveprice increased on average by 110%	oct-06	+1
France	In addition to the 15% price cuts planned for Feb 2006 for all generics (an additional 4% will be cut) and their corresponding original off-patent products (additional 10% will be cut). New generics will be required to be priced at 50% below the branded drug instead of 40-50% lower starting Jan 2006.	dec-05	-1
Spain	The CIPM raised the minimum price difference required for the first generic to 40% (from 30%) below the ex-factory price of the original brand	july-10	-1
Spain	Retail price cuts ranging from 0-30% and revised prices for generic products take effect 15 days after the April 17th publication.	apr-10	-1
Spain	Update to reference price system	oct-09	0
Spain	New "cheapest price" list implemented. Will be updated annually.	july-09	0
Spain	Update to reference price system	march-08	0
Spain	New reference price order setup in Mar-07 causes Spanish regions to stop applying regional max price reimbursement systems	apr-07	0

Spain	269 reference priced presentations delisted after interpretation error over the new reference price order. Manufacturers thought the Health Ministry would automatically reduce the prices of their products with no identical alternatives, but the government was expecting to receive the new prices.	march-07	0
Spain	Andalucia updates the reference price list effective Jan 2006. 129 presentations will decrease while 5 will increase.	jan 06	-1
Spain	Ex-manufacturer selling prices of almost 4,500 medicines marketed for over one year will be cut by 4.2% in 2005 and by 2% in 2006	jan-05	-1
Italy	Generics subject to 12.5% public price cuts effective June 2010	july-10	-1
Italy	Generics subject to 12% public price cuts effective May 2009	june-09	-1
Italy	Premium prices for products manufactured by companies with R&D/production sites in Italy	nov-08	0
Italy	Price cuts to be extended into 2007	sept-06	0
Italy	New price cuts of 0.6% on public price to cover the 2005 pharmaceutical overspend	july-06	-1
Italy	4.4% price cuts on public price	jan-06	-1
Germany	Price freeze on all reimbursed drugs	august-10	-1
Germany	Two-year price freeze on all pharmaceuticals ends as scheduled	march-08	+1
Germany	New reference prices for eight new reference price groups	july-07	0
Germany	The prices of more than 1,600 products were reduced	febr-05	-1
Germany	Member companies of the generics association Pro Generika (accounting for 90% of generic sales) voluntarily pledge to implement a price freeze on prescription generis until Dec 31, 2005	jan-05	0

Netherlands	Preference policy has led generic manufactures to cut their pharmacy purchase prices by an average of 85% within the official price list for June 2008 in order to remain competitive	may-08	-1

Therapeutic Area	Country	Impact	Date	Expected Price Impact
Lipid Regulators	Germany	The SK has decided on new reference prices for statins effective January 1, 2005.	nov-04	-1
ACE inhibitors Antiulcerant Antidepressant	France	Generic price cuts of the branded and generic versions of enalapril reduced by roughly 14%; omeprazole generic versions extended from roughly 32% to 41% cheaper than the off-patent drug; fluoxetine generics extended from 31.5% to 39% cheaper.	febr-05	-1
Lipid Regulators ACE Inhibitors Antiulcerants	Italy	The AIFA has approved the revised reimbursement list, effective Jan. 1, 2005. The revision comprises a price reduction for those drugs which in 2004 have registered sales increases in excess of 8.6%. (statins, proton pump inhibitors, sartans, diuretics and acid inhibitors are among those hit by price cuts)	jan 05	-1
Lipid Regulators	Germany	16 regional associations of AOKs have signed a comprehensive discount agreement on selected drugs - including ACE inhibitors, statins, calcium antagonists and proton pump inhibitors - with 11 generic manufacturers	févr-07	-1
Lipid Regulators	France	Targeted drug price cuts will be implemented in autumn 2010 and will primarily affect sartans, erythropoietins, anti-TNF-alpha therapies and high-dose statins	juen-07	-1
Lipid Regulators	France	Targeted price cuts planned for autumn. The price cuts will primarily affect "sartans, erythropoietins, anti-TNF-alpha therapies and high-dose statins	June 10	-1
Lipid Regulators	Germany	Comprehensive rebate deal covering 82 active ingredients expected to take effect in 2008 and last for 2 years	july-07	-1

Lipid Regulators	France	Price cuts for patented medicines in therapeutic classes where a generic exists were published on Nov 29, 2006. In total 12 active ingredients corresponding to six therapeutic classes will be impacted, including PPIs, statins, anti-histamines, anti-depressants, ACE inhibitors and prostatic hypertrophy treatments. Price cuts will reach up to 15%.	dec-06	-1
Lipid Regulators	Netherlands	Effective January 1, 2009, physicians need to start new statin patients on the preferred off-patent drugs, simvastatin or pravastatin to ensure reimbursement. This preference policy led to massive generic price cuts.	jan 09	-1
Lipid Regulators	Spain	Andalucia has reintroduced a regional max price reimbursement scheme for atorvastatin.	Feb 10	-1
Antiulcerants	Germany	The SK has decided on new reference prices for statins effective January 1, 2005.	nov-04	-1
Specific Drugs	France	Zocor (simvastatin) will have its price reduced by 6-7%, depending on the dosage in May 2005. Generic versions of the simvastatin drug will now be required to be even cheaper.	march-05	-1
Antiulcerants Antidepressants	Italy	A temporary and selected reduction of drug prices effective Jul 2006 include reductions up to 10% for proton pump inhibitors, corticosteroids, NSAIDs, anti-asthmatics, anti-epileptics and SSRI antidepressants.	july-06	-1
Antiulcerants Lipid regulators Antidepressants Ace inhibitor	France	Price cuts for patented medicines in therapeutic classes where a generic exists were published on Nov 29, 2006. In total 12 active ingredients corresponding to six therapeutic classes will be impacted, including PPIs, statins, anti-histamines, anti-depressants, ACE inhibitors and prostatic hypertrophy treatments. Price cuts will reach up to 15%.	dec-06	-1
Antiulcerants Ace inhibitors Calcium channel blockers	Germany	16 regional associations of AOKs have signed a comprehensive discount agreement on selected drugs - including ACE inhibitors, statins, calcium antagonists and proton pump inhibitors - with 11 generic manufacturers	febr-07	-1
Antiulcerants	Italy	Disagreement over the legal status of the regional therapeutic reference pricing systems for the proton pump inhibitors.	june-07	0

Antipsychotics	Germany	The Federal Association o f Health Insurance Funds has set reference prices for the new level 2 (pharmacologically/therapeutically comparable active ingredients) group, other antipsychotics. This reference group consists of Invega and off-patent risperidone. Invega will not lower its price to the reference price level because it would result in an 85% price cut.	sept-09	-1
Antidepressants Antiulcerants	Italy	A temporary and selected reduction of drug prices effective Jul 2006 include reductions up to 10% for proton pump inhibitors, corticosteroids, NSAIDs, anti-asthmatics, anti-epileptics and SSRI antidepressants.	july-06	-1
Antidepressants	France	Price cuts for patented medicines in therapeutic classes where a generic exists were published on Nov 29, 2006. In total 12 active ingredients corresponding to six therapeutic classes will be impacted, including PPIs, statins, anti-histamines, anti-depressants, ACE inhibitors and prostatic hypertrophy treatments. Price cuts will reach up to 15%.	dec-06	-1
Osteoporosis	France	The first three-month pack available on the French market will be the osteoporosis drug Actonel (risedronate) starting in mid-August 2005.	july-05	0
Osteoporosis	Germany	The Baden-Wurttemberg regional association of local health insurance funds and the manufacturer MSD Sharp & Dohme have signed a discount deal covering three patented products. The osteoporosis drug Fosavance (alendronate and colecalciferol) is one of these products that will have price reductions.	may-08	-1
Osteoporosis	Germany	The private insurer Barmenia and the manufacturer Daiichi Sankyo have signed a discount deal covering two patented products. The osteoporosis drug Evista (raloxifene) is one of these products that will have price reductions.	juyl-08	-1
Osteoporosis	France	Three-month packs of medicines introduced to treat four chronic conditions. On average 13% cheaper than monthly packs.	febr-10	-1
Calcium Channel Blockers	Germany	16 regional associations of AOKs have signed a comprehensive discount agreement on selected drugs - including ACE inhibitors, statins, calcium antagonists and proton pump inhibitors - with 11 generic manufacturers	febr-07	-1

Calcium Channel Blockers	Germany	The SK has set 13 new reference price groups. ACE inhibitor and calcium channel blocker combinations fall under level 3 (drugs with therapeutically comparable effects). These will take effect Jan 1, 2008.	sept-07	0
ACE Inhibitors	France	Ex-factory prices of 38 3-month drug packs will be cut by around 5%. Many of which are antihypertensives and ACE inhibitors.	febr-09	-1
ACE Inhibitors	Germany	16 regional associations of AOKs have signed a comprehensive discount agreement on selected drugs - including ACE inhibitors, statins, calcium antagonists and proton pump inhibitors - with 11 generic manufacturers	febr-07	-1
ACE Inhibitors	Germany	The SK has set 13 new reference price groups. ACE inhibitor and calcium channel blocker combinations fall under level 3 (drugs with therapeutically comparable effects). These will take effect Jan 1, 2008.	jan-08	0
ACE Inhibitors	France	Price cuts for patented medicines in therapeutic classes where a generic exists were published on Nov 29, 2006. In total 12 active ingredients corresponding to six therapeutic classes will be impacted, including PPIs, statins, anti-histamines, anti-depressants, ACE inhibitors and prostatic hypertrophy treatments. Price cuts will reach up to 15%.	dec-06	-1
Beta Blockers	Germany	Barmer health insurance fund and Merck Pharma have signed a new discount agreement. Merck will grant price discounts for its beta blockers: Concor, Concor COR and Concor plus.	dec-05	-1

APPENDIX B: ECONOMETRIC FINDINGS BASED ON ALTERNATIVE SPECIFICATIONS

Table B1: Regressions with Laspeyres Chained Indices

Therapeutic Class Level of Aggregation, Country*Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.000119**	-0.000115**
	(5.06e-05)	(5.09e-05)
sh_expired	-0.0205**	
	(0.00832)	
sh_expired_pharma		-0.0236**
		(0.00976)
sh_expired_physic		-0.0175**
		(0.00740)
Regulatory Changes		
ac_price_impact	0.000908	0.00123
	(0.00135)	(0.00141)
ac_price_impact_tcl	0.00106	0.000377
	(0.00153)	(0.00194)
Constant	0.00514	0.00534
	(0.00491)	(0.00480)
Observations	7,095	7,095
R-squared	0.013	0.014
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table B2: Regressions with Paasche Chained Indices

Therapeutic Class Level of Aggregation, Country*Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.00102***	-0.00100***
	(0.000279)	(0.000279)
sh_expired	-0.0312	
	(0.0307)	
sh_expired_pharma		-0.0424
		(0.0341)
sh_expired_physic		-0.0201
		(0.0318)
Regulatory Changes		
ac_price_impact	-0.0163**	-0.0151*
	(0.00762)	(0.00769)
ac_price_impact_tcl	0.00632	0.00383
	(0.00427)	(0.00452)
Constant	0.0370***	0.0377***
	(0.0139)	(0.0139)
Observations	7,095	7,095
R-squared	0.028	0.029
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table B3: Regressions with Laspeyres (fixed US January 2004 = 1.00 basis) Indices

Therapeutic Class Level of Aggregation, Country*Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.00896***	-0.00883***
	(0.00122)	(0.00119)
sh_expired	-1.126***	
	(0.210)	
sh_expired_pharma		-1.243***
		(0.253)
sh_expired_physic		-1.009***
		(0.173)
Regulatory Changes		
ac_price_impact	-0.0201	-0.00782
	(0.0230)	(0.0201)
ac_price_impact_tcl	0.0140	-0.0121
	(0.0192)	(0.0265)
Constant	0.0634	0.0713
	(0.130)	(0.131)
Observations	7,183	7,183
R-squared	0.621	0.626
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table B4: Regressions with Paasche (fixed US January 2004 = 1.000 basis) Indices

Therapeutic Class Level of Aggregation, Country*Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.00978***	-0.00967***
	(0.00138)	(0.00135)
sh_expired	-1.238***	
	(0.259)	
sh_expired_pharma		-1.337***
		(0.315)
sh_expired_physic		-1.139***
		(0.214)
Regulatory Changes		
ac_price_impact	-0.0869***	-0.0764***
	(0.0295)	(0.0256)
ac_price_impact_tcl	0.0248	0.00265
	(0.0241)	(0.0321)
Constant	0.145	0.152
	(0.162)	(0.164)
Observations	7,183	7,183
R-squared	0.593	0.596
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table B5: Regressions with Fisher (fixed US January 2004 = 1.000 basis) Indices

Therapeutic Class Level of Aggregation, Country*Class Fixed Effects

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.00937***	-0.00925***
	(0.00124)	(0.00121)
Sh_expired	-1.182***	
	(0.232)	
sh_expired_pharma		-1.290***
		(0.282)
sh_expired_physic		-1.074***
		(0.191)
Regulatory Changes		
ac_price_impact	-0.0535**	-0.0421*
	(0.0252)	(0.0217)
ac_price_impact_tcl	0.0194	-0.00473
	(0.0202)	(0.0282)
Constant	0.104	0.112
	(0.144)	(0.146)
Observations	7,183	7,183
R-squared	0.628	0.632
Country-Class FE	Yes	Yes

Standard errors clustered by country-class

Table B6: Regressions with Laspeyres (fixed US January 2004 = 1.000 basis) Indices
Country and Class Fixed Effects, not Country*Class
Therapeutic Class Level of Aggregation

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.00950***	-0.00946***
	(0.00168)	(0.00167)
sh_expired	-0.915***	
	(0.155)	
sh_expired_pharma		-0.981***
		(0.210)
sh_expired_physic		-0.806***
		(0.114)
Regulatory Changes		
ac_price_impact	-0.0140	-0.00412
	(0.0202)	(0.0219)
ac_price_impact_tcl	0.0142	-0.00534
	(0.0153)	(0.0270)
Country Dummies (reference is US)		
CANADA	-0.0585	-0.0607
	(0.171)	(0.169)
FRANCE	-0.397**	-0.457**
	(0.149)	(0.160)
GERMANY	-0.603***	-0.714**
	(0.163)	(0.230)
ITALY	-0.591**	-0.698**
	(0.211)	(0.230)
NETHERLANDS	-0.704***	-0.701***
	(0.204)	(0.206)
SPAIN	-0.745***	-0.842***
	(0.165)	(0.175)
UK	-0.762***	-0.758***
	(0.182)	(0.184)
Constant	0.431**	0.473**
	(0.178)	(0.191)
Observations	7,183	7,183
R-squared	0.516	0.518
Class FE	Yes	Yes

Standard errors clustered by country-class

Table B7: Regressions with Paasche (fixed US January 2004 = 1.000 basis) Indices
Fixed Effects by Country and Class, not Country*Class
Therapeutic Class Level of Aggregation

OLS	(1)	(2)
VARIABLES	$log\pi_{knt}$	$log\pi_{knt}$
Time trend (monthly)	-0.0105***	-0.0105***
	(0.00198)	(0.00199)
sh_expired	-0.959***	
	(0.131)	
sh_expired_pharma		-0.980***
		(0.216)
sh_expired_physic		-0.924***
		(0.105)
Regulatory Changes		
ac_price_impact	-0.0788***	-0.0756**
	(0.0234)	(0.0277)
ac_price_impact_tcl	0.0251	0.0188
	(0.0141)	(0.0303)
Country Dummies (reference is US)		
CANADA	0.0827	0.0820
	(0.162)	(0.162)
FRANCE	-0.176	-0.195
	(0.198)	(0.199)
GERMANY	-0.495*	-0.531
	(0.266)	(0.345)
ITALY	-0.398	-0.433
	(0.242)	(0.288)
NETHERLANDS	-0.580**	-0.579**
	(0.213)	(0.214)
SPAIN	-0.708**	-0.739**
	(0.237)	(0.236)
UK	-0.777***	-0.776***
	(0.242)	(0.242)
Constant	0.377*	0.390
	(0.197)	(0.216)
Observations	7,183	7,183
R-squared	0.444	0.444
Class FE	Yes	Yes

Standard errors clustered by country-class

ENDNOTES

[1] See, for example, Danzon and Chao [2000b] and Danzon and Furukawa [2011, 2008, 2003].

[2] See, for example, for the US, Aitken, Berndt and Cutler [2008], Berndt and Aitken [2011], Berndt, McGuire and Newhouse [2011], Cook [1998], Grabowski and Kyle [2007], IMS Institute for Healthcare Informatics [2011], Reiffen and Ward [2007,2005], Saha, Grabowski, Birnbaum, Greenberg and Bizan [2006], and Scott Morton [2000]; for Canada, Hollis [2002] and Jones, Potashnik and Zhang [2001]; for France, Paraponaris, Verger, Desquins, Villani, Bouvenot, Rochaix, Gourheux and Moatti [2004]; for Germany, Appelt [2009]; and for Spain, Lopez-Bastida and Mossialos.

[3] See, for example, Danzon-Chao [2000b], Danzon-Furukawa [2011, 2008], Garattini and Tediosi [2000] and Hudson [2001].

[4] Danzon-Chao [2000a,b], Danzon-Furukawa [2011,2005], and United States Department of Commerce [2004].

[5] These include, among others, Appelt [2009], Berndt, Cockburn and Griliches [1996], Berndt, Kyle and Ling [2003], Ellison and Ellison [2011], Federal Trade Commission [2011,2009], Frank and Salkever [1997,1992], Grabowski and Kyle [2007], Hemphill and Sampat [2011], Huskamp, Donohue, Koss, Berndt and Frank [2008], Kyle [2010,2009,2007], Reiffen and Ward [2007], and Scott Morton [2000].

[6] Danzon-Chao [2000a] and Manning [1997].

[7] Danzon-Furukawa [2011], Kyle [2009, 2007], Appelt [2011].

[8] Danzon-Furukawa [2011], and Paraponaris, Verger, Desquins, Villani, Bouvenot, Rochaix, Gourheux and Moatti [2004].

[9] Studies with these foci include Aitken-Berndt [2011], Aitken, Berndt and Cutler [2008], Appelt [2009], Berndt and Aitken [2011], Berndt, Cockburn and Griliches [1996], Berndt, Kyle and Ling [2003], Cook [1998], Danzon-Furukawa [2011,2008], Ellison, Cockburn, Griliches and Hausman [1997], Frank and Salkever [1997,1992], Grabowski and Kyle [2007], Griliches and Cockburn [1994], Kyle [2007], Reiffen and Ward [2005], and Saha, Grabowski, Birnbaum, Greenberg and Bizan [2006].

[10] For discussion and analyses of parallel imports, see Danzon-Chao [2000a], Kyle [2010, 2009] and the references cited therein.

[11] Within the IMS classification scheme, a US example of (i) is Concerta™, an extended release formulation of methylphenidate hydrochloride, the active ingredient in the off-patent drug Ritalin™ commonly used to treat attention deficit hyperactivity disorder, while the opiod analgesic pain reliever Oxycontin™ is an example of (iii).

[12] Berndt and Aitken [2011], Table 1.

[13] For a discussion of strategic issues involving branded generics in the US context, see Reiffen and Ward [2007].

[14] For an overview of the procedures employed by the US Bureau of Labor Statistics in constructing pharmaceutical price indexes, see Berndt, Cutler, Frank, Griliches, Newhouse and Triplett [2000], especially pp. 150-3 and 158.

[15] World Health Organization [2009], pp. 1,2; italics and bold in original text. For further details concerning DDD, see World Health Organization [2003 (Ch. 6), 2011]; also International Federation of Pharmaceutical Manufacturers & Associations [2006].

[16] We thank Murray Aitken and Michael Kleinrock from IMS Health for making this data analysis available to us.

[17] In preliminary specifications, we added annual indicator variables; since parameter estimates on these year indicator variables were jointly statistically insignificant, we omit them.