

Cross-national price differences for pharmaceuticals: how large, and why?

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Abstract

Bilateral drug price and quantity indexes, based on comprehensive data for seven countries (US, Canada, France, Germany, Italy, Japan and the UK), refute the conventional wisdom that US drug prices are much higher than elsewhere, for Laspeyres (US-weighted) indexes. Previous drug-price comparisons are biased by unrepresentative samples and unweighted indexes. Quasi-hedonic regression shows that cross-national price differences reflect differences in product characteristics and in their implicit prices, which reflect the regulatory regime. Strict price regulation systematically lowers prices for older molecules and globally diffused molecules. Generic competition lowers prices in less-regulated regimes, which also have more price-elastic demand. © 2000 Elsevier Science B.V. All rights reserved.

1. Introduction

Accurate measurement of cross-national price differences for drugs is an important policy and research issue. Cross-national comparisons of drug prices are often used to evaluate the performance of different regulatory systems. The General Accounting Office's comparison of drug prices in the US relative to Canada and the UK concluded that US prices were 32% higher than Canada and 60% higher than the UK (U.S. General Accounting Office, 1992, 1994). The

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Minority Staff (U.S. House of Representatives, 1998) concluded that US prices were 70% higher than Canada and 102% higher than Mexico. These studies appear to support the view that US drug prices are much higher than the rest of the world's, and have contributed to proposals for drug price controls — for example, President Clinton's Health Security Act (U.S. Government Printing Office, 1993) and the Prescription Drug Fairness Act of 1999 (H.R. 644). In addition to these comparisons of average price levels, a growing number of countries, including Italy, Spain, the Netherlands, Canada, and Japan, use international comparisons in their regulation of prices for individual drugs.

Previous cross-national drug price comparisons have been biased due to the use of inappropriate index methods applied to small, non-random samples of branded products, omitting all generics. For example, the Minority Staff Report (1998) compared retail prices in the US relative to Canada or Mexico based on the unweighted average of the price ratios for 10 leading originator drugs, using a single pack per drug. The U.S. General Accounting Office (1992) US–Canada comparison reported the price in the US relative to the price in Canada for a market basket consisting of one pack of each of 121 leading brand products, unweighted. U.S. General Accounting Office (1994) used 77 products in its US–UK comparison. The OECD purchasing power parities (PPPs) for drugs and medical devices (OECD, 1993) are also based on small, unrepresentative samples for each country, use inappropriate imputation for missing prices and lack weights to reflect the relative importance of different products.¹

The purpose of this paper is threefold. First, we report indexes of manufacturer-level drug prices for six countries — Canada, France, Germany, Italy, Japan and the UK — relative to the US, using more comprehensive data and more appropriate methods than those used in previous studies. Our sample is based on Intercontinental Medical Systems (IMS) data for all outpatient drug sales in 1992.² For all molecules that match across the countries under comparison, we compute a weighted average price per gram or price per dose, including all products in the molecule — originator, licensed, and generic — and all formulations, strengths and packs for each molecule. Using this more comprehensive sample, our Laspeyres (US quantity weighted) indexes for price per dose show foreign/US differences as follows: Canada +2.1%; Germany +24.7%; France –32%; Italy –13%; Japan –12%, and the UK –17%. Thus, with the expanded sample and weighted indexes, the differences across countries in average drug-price levels are not as great as suggested by previous studies that used small samples of leading branded products and unweighted averages.

¹ The retail prices used by the Minority Staff and OECD PPPs cannot provide a valid measure of manufacturer prices due to distribution margins and VAT, which differ across countries.

² Intercontinental Medical Systems (IMS) is a market research firm that collects data on drug sales worldwide.

Second, since estimates of price differences are very sensitive to the index measure used, we examine the factors inherent in these index measures that contribute to the different estimates. The ratio of each country's Paasche (own weighted) index relative to its Laspeyres (US weighted) index is consistently less than one, ranging from 0.32 for Germany to 0.67 for the UK. This tendency, for each country to appear cheaper using own-weighted indexes rather than comparison-weighted indexes is independent of whether the US or another country is used as the base. Known as the Gerschenkron effect, it has been found in indexes of intertemporal and cross-sectional price and quantity changes in other industries (for example, Gerschenkron, 1947; Gerschenkron and Erlich, 1951; Jonas and Sardy, 1972; Kravis et al. 1982; Van Ark et al. 1996).³ The excess of Laspeyres indexes over Paasche indexes might simply reflect a substitution effect, assuming that consumers in each country use relatively more of those products that are relatively cheap in that country. However, the Bortkiewicz formula (von Bortkiewicz, 1922, 1924; Allen, 1975) shows that although a negative correlation between price and quantity relatives is necessary and sufficient for $P/L < 1$, the magnitude of the P/L differential also depends on the dispersion in price and quantity relatives:

$$P_P/L_P \equiv P_Q/L_Q \equiv 1 + (r_{xy}v_xv_y) \quad (1)$$

where r_{xy} is the weighted coefficient of correlation between price and quantity relatives, v_x is the weighted coefficient of variation of price relatives, and v_y is the weighted coefficient of variation of quantity relatives, with all components measured as deviations from the base-weighted index.

We estimate these components for our drug price distributions and find that the P/L differentials for drug prices are dominated by dispersion across molecules in each country's price and quantity relatives with the US. The coefficients of variation for price relatives v_x range from 0.72 in Canada to 14.6 in Japan. Thus, the effect of regulation (or other country-specific factors) is not simply to reduce all prices by a uniform percentage relative to unregulated US prices (in which case, v_x would be zero). By contrast, the correlation between price and quantity relatives r_{xy} , one possible measure of substitution effects, is negative but small, ranging from -0.001 in Japan to -0.106 in the UK.

The third purpose of this paper is to analyze the determinants of the variation in price relatives across molecules for each country relative to the US. We use quasi-hedonic regression to measure the contribution of product and market characteristics to prices in different countries, with a fully interacted model that permits intercepts and parameters (implicit prices of characteristics) to differ

³ Most studies have attributed the Paasche/Laspeyres (P/L) discrepancy for intertemporal comparisons to intersectoral shifts that occur during the industrialization process. This hypothesis cannot explain our cross-national findings for drug prices.

across countries (for example, Kravis and Lipsey, 1971). This analysis finds that countries with strict price regulation (France, Italy, and Japan) systematically have lower prices for older molecules and for global products (a rough measure of therapeutic value), relative to less-regulated regimes such as the US and the UK. By contrast, generic competition operates as a more effective control on prices in less regulated regimes, particularly the US, which have both more generic competitors and more price competition between competitors than do regulated regimes. Given these systematic effects on relative prices of molecule age, therapeutic value and generics, an important implication for policy is that unbiased cross-national price comparison requires a sample that is representative along all these dimensions.

An important implication of our analysis for the methodology of price measurement is that standard hedonic regression methods do not strictly apply to measurement of cross-national drug price differences. Standard cross-area hedonic regression treats variation across areas in product characteristics as random, hence area intercepts can be interpreted as pure area effects (for example, Kokoski, 1991). However, in cross-country hedonic regression for drug prices, measured characteristics and their implicit prices are themselves influenced by each country's regulatory system, hence, differences in mean characteristics and their implicit prices are key to understanding the determinants of measured price differences. Country intercepts reflect only unmeasured country effects.

As noted earlier, there is considerable dispersion across molecules in the quantity relatives, $q_{j,S}/q_{j,US}$, which measure quantity consumed of each j th molecule in country S relative to the US. Indeed, the weighted coefficient of variation of quantity relatives is the single most important contributor to the differences between Laspeyres and Paasche indexes. We test whether differences across molecules in relative quantities can be partly explained by differences in their relative prices in country S , compared to the US. Our two-stage least squares estimates show significant negative own price elasticities (at the molecule level), ranging from -1.3 for the US, Canada, and Germany, to -0.36 for Italy. We conclude that there is some evidence of substitution towards molecules that are relatively cheap in each country, despite the low correlation between absolute price and quantity relatives r_{xy} , which partly reflects their right-skewed distributions. A full analysis of cross-national quantity differences is an important topic but beyond the scope of this paper.

The structure of the paper is as follows: Section 2 describes the data and methods. Section 3 reports Laspeyres and Paasche price and quantity indexes for the six countries relative to the US, and the Bortkiewicz decomposition into coefficients of correlation and variation. Section 4 reports quasi-hedonic regression analysis of log price relatives and estimates of demand elasticities. Section 5 uses the regression estimates to summarize the contribution of cross-national differences in product characteristics and their parameter effects to the mean price ratio for each country relative to the US. Section 6 concludes.

2. Data and methods

Accurate measurement of both cross-national and intertemporal price indexes for drugs is problematic because of the broad range of products, multidimensional quality and rapid technological change. Previous studies have focused on the measurement of intertemporal price change within the US. Berndt et al. (1993) show that fixed weight indexes, which delay the incorporation of new drugs, lead to upward biased measures of price inflation. Griliches and Cockburn (1994) address the problem of incorporating generic versions of old drugs. Suslow (1996) demonstrates the importance of quality differences, using hedonic regression applied to anti-ulcer drugs.

In the cross-national context, problems arising from diversity of products are more extreme. In our seven countries — Canada, France, Germany, Italy, Japan, the UK, and the US — less than one third of each country's molecules are present in all seven markets. Drugs with the same active ingredient may differ in dosage forms, strengths and packsizes across countries, and are produced by different manufacturers — originator, licensed, or generic producer — and sometimes in prescription and over-the-counter form. This diversity within and between countries implies a trade-off: if price comparisons are confined to products that are identical in chemical composition, manufacturer, formulation, strength and packsize, as attempted in previous studies, then only a small and unrepresentative sample of each country's products can be included, and most generics will be excluded. Most previous cross-national price comparisons (for example, U.S. General Accounting Office, 1992, 1994; Bureau European des Unions Consommateurs (BEUC), 1989a,b) have exacerbated this intrinsic problem of nonmatching products by intentionally selecting only leading branded prescription products.

This study draws data from a comprehensive IMS database of all drug sales through retail pharmacies between October 1991 and September 1992. We define a drug by active ingredient (molecule) and the anatomic therapeutic category (ATC) at the three-digit level (ATC3) to which the drug is classified, regardless of manufacturer or brand name. We report indexes for two samples. The bilaterally matched sample includes, for each country, all molecules that are available in both the US and the comparison country, ranging from 365 molecules for the Japan–US comparison to 438 for the Germany–US comparison. The global sample includes the 171 molecules that are available in all seven countries, hereafter “global molecules”.⁴ The price for each molecule is defined as a weighted average price,

⁴ These bilateral and global samples are matched using molecule name and ATC3 as matching criteria. For a few molecules, different strengths and/or forms are classified by IMS to different ATCs, implying use for different indications. These are appropriately treated as distinct products because market and regulatory conditions may differ across ATCs. In fact, indexes based on the simple molecule, regardless of ATC, are very similar to those obtained from molecule/ATC3 matched samples presented in this paper.

based on all products in the molecule, including originator, licensed, generic and those OTC products that meet the sample selection criteria.⁵ This weighted average price per molecule implicitly assumes that all products with the same active ingredient and for the same indication are perfect substitutes, regardless of originator/generic status, manufacturer, or prescription/OTC status. This assumption of perfect substitutability is consistent with practices of third-party payers in the US, Canada, Germany, Sweden, the UK, and other countries, who set a single reimbursement price for all generically equivalent products, regardless of real and perceived differences between originator and generic products (see Griliches and Cockburn, 1994).

Our prices are at the manufacturer level, except that the US price data do not reflect manufacturers discounts given directly to managed care and public purchasers, or sales through mail order, supermarkets, and HMOs. Similarly, the UK data do not reflect all discounts given to pharmacists.⁶ Thus, IMS list prices for the US and the UK in 1992 may significantly overestimate actual manufacturer prices for certain products, as discussed further below. We use two measures, price per gram of active ingredient (KG) and price per IMS “standard unit” (SU). A standard unit is defined by IMS as one tablet, one capsule, 10 ml of a liquid, etc., and is a rough proxy for a dose. There is no perfect measure of a quality-constant course of drug therapy.⁷ However, the advantage of standard units and grams is that they are defined for all formulations and packs, hence, our weighted average price for the molecule incorporates all forms and packs of that molecule. By contrast, previous cross-national drug price studies have compared prices for a single “representative” pack, for example, a pack of one hundred 250-mg tablets, sometimes with linear imputation where the same pack was not available in all countries. As shown below, since mean strength and packsize, and

⁵ We exclude products with sales of less than 1000 packs or 1 kg of active ingredient, because of higher risk of sampling and reporting error. Multiple molecule drugs are excluded because the relative mix of the different molecules is not necessarily the same in all countries. Since OTC status is not identified, the sample includes some OTC products, and this is appropriate assuming they are good substitutes for prescription-bound products.

⁶ In the US, between first quarter 1991 and 1993, the median best price discount declined from 24% to 14% for HMOs (U.S. General Accounting Office, 1994); the unweighted average best price discounts declined from 42% in first quarter 1991 to 33.4% in fourth quarter 1992 (U.S. Congressional Budget Office (CBO), 1996). For the UK, an April 1992 Department of Health Pharmacist Discount Enquiry showed generic prices on average 47.7% below the NHS drug tariff (of which 12.5% is the wholesale margin). Following deep reductions in NHS prices, an April 1993 Pharmacist Discount Enquiry found average discounts of only 26%.

⁷ Other studies have used price per WHO defined daily dose (DDD), which is not available to us. DDDs are also imperfect because they are not defined to be equipotent units, do not necessarily correspond to actual daily doses, and ignore differences in duration of treatment (Danzon, 1996). Since DDDs for each drug are defined as grams per day, indexes based on DDDs should be similar to our indexes based on grams, if days of treatment are uniform across countries.

their implicit prices differ systematically across countries, serious bias can result from including only a single pack and using linear imputation based on price per pill in other packs if the selected pack is not available.⁸

Although we require only that the molecule/ATC3 match across countries, not the same manufacturer or packsize, nevertheless, over 40% of total retail pharmacy sales in Germany, France, Italy, and Japan do not match and cannot be included even in our larger, bilaterally matched samples. This heterogeneity in product-mix across countries implies that even the price indexes, which start with the universe of sales may be unavoidably biased because they are confined to matching molecules.

3. Laspeyres and Paasche price and quantity indexes

3.1. Price and quantity indexes

Table 1 reports price and quantity indexes for the two volume measures, standard units (SU) and grams (KG), for each of the six comparison countries relative to the US, using US weights (Laspeyres) and comparison country weights (Paasche). Also reported are the Paasche/Laspeyres ratios, which are identical for price and quantity indexes. The indexes in Parts A and B are, respectively, for bilaterally matched products and global products. The Laspeyres indexes, which may be most relevant from the US perspective since they use US weights, can be interpreted as a lower-bound estimate of how much the US might save by adopting another country's prices, assuming no change in US consumption patterns. The Paasche indexes provide an upper-bound estimate of potential savings, under the implausible assumption that the US would adopt the other country's consumption patterns, and that such changes in US prices and volumes would not affect R&D.

3.1.1. Price indexes

The Laspeyres indexes for price per standard unit show smaller price differences than reported in other studies: Canada and Germany, respectively, are 2.1% and 24.7% higher than the US; Japan, Italy, and the UK are respectively 11.6%, 12.9%, and 16.6% lower than the US; and France is 32.2% lower than the US. With the Paasche indexes, all countries appear to have lower prices than the US, ranging from 44% lower for the UK to 67% lower for France. Thus, both the magnitude and the rank ordering of price differentials depend on the weights. For given weights, the SU and KG indexes differ significantly for some countries, due to systematic difference in grams per standard unit. Strength per dose in Japan, for example, is typically weak, in part because doctors commonly prescribe several drugs to be taken together (polypharmacy). Japan thus appears 11.6% less

⁸ Linear imputation can lead to bias because price per pill is not linear in packsize and both mean packsize and the price–packsize relation differ across countries (see Table 2 below).

Table 1
Pharmaceutical price indexes relative to US — 1992 molecule/ATC matching

a. Bilateral matches with US

Index/Variable		Canada	Germany	France	Italy	Japan	UK
Number of molecules		420	438	373	386	365	377
Laspeyres price index	(KG)	0.866	0.914	0.548	0.696	1.193	0.713
Laspeyres price index	(SU)	1.021	1.247	0.678	0.871	0.884	0.834
Paasche price index	(KG)	0.674	0.597	0.419	0.326	0.484	0.522
Paasche price index	(SU)	0.447	0.403	0.330	0.485	0.457	0.560
Laspeyres quantity index ^a	(KG)	1.320	1.145	2.122	2.353	1.019	1.026
Laspeyres quantity index ^a	(SU)	1.989	1.694	2.690	1.583	1.081	0.957
Paasche quantity index ^a	(KG)	1.027	0.748	1.621	1.103	0.414	0.752
Paasche quantity index ^a	(SU)	0.871	0.548	1.311	0.881	0.559	0.642
Population ratio (foreign/US)		0.103	0.244	0.218	0.220	0.473	0.219
Paasche/Laspeyres	(KG)	0.778	0.653	0.764	0.469	0.406	0.733
Paasche/Laspeyres	(SU)	0.438	0.323	0.487	0.557	0.517	0.671
r_{xy}	(KG)	-0.095	-0.006	-0.033	-0.011	-0.001	-0.106
v_x	(KG)	0.723	5.801	0.995	1.163	14.606	0.875
v_y	(KG)	3.241	9.972	7.154	42.262	77.209	2.872
r_{xy}	(SU)	-0.001	-0.008	-0.002	-0.027	-0.043	-0.047
v_x	(SU)	4.383	3.588	2.483	1.524	1.967	1.677
v_y	(SU)	124.321	24.664	129.718	10.758	5.689	4.172
$r_{xy} * v_x * v_y$	(KG)	-0.222	-0.347	-0.236	-0.531	-0.594	-0.267
$r_{xy} * v_x * v_y$	(SU)	-0.562	-0.677	-0.513	-0.443	-0.483	-0.329

b. All seven country matches

Index/Variable		Canada	Germany	France	Italy	Japan	UK
Number of molecules		171	171	171	171	171	171
Laspeyres price index	(KG)	0.857	0.887	0.576	0.696	1.163	0.708
Laspeyres price index	(SU)	0.983	1.193	0.701	0.910	0.943	0.883
Paasche price index	(KG)	0.699	0.589	0.427	0.302	0.792	0.553
Paasche price index	(SU)	0.694	0.362	0.364	0.543	0.479	0.630
Laspeyres quantity index ^a	(KG)	1.349	1.207	2.038	2.290	0.566	1.055
Laspeyres quantity index ^a	(SU)	1.358	1.966	2.392	1.276	0.936	0.927
Paasche quantity index ^a	(KG)	1.100	0.802	1.511	0.995	0.386	0.824
Paasche quantity index ^a	(SU)	0.959	0.596	1.242	0.761	0.476	0.661
Population ratio (foreign/US)		0.103	0.244	0.218	0.220	0.473	0.219
Paasche/Laspeyres	(KG)	0.815	0.664	0.741	0.435	0.681	0.781
Paasche/Laspeyres	(SU)	0.706	0.303	0.519	0.596	0.508	0.713
r_{xy}	(KG)	-0.094	-0.036	-0.035	-0.010	-0.044	-0.093
v_x	(KG)	0.569	0.919	0.925	1.102	1.863	0.892
v_y	(KG)	3.434	10.284	8.082	51.084	3.889	2.622
r_{xy}	(SU)	-0.034	-0.015	-0.020	-0.024	-0.061	-0.044
v_x	(SU)	2.009	1.809	1.102	1.467	1.942	1.804
v_y	(SU)	4.284	25.239	21.935	11.345	4.129	3.580
$r_{xy} * v_x * v_y$	(KG)	-0.185	-0.336	-0.259	-0.565	-0.319	-0.219
$r_{xy} * v_x * v_y$	(SU)	-0.294	-0.697	-0.481	-0.404	-0.492	-0.287

(continued on next page)

Table 1 (continued)

	c. Contribution of sample and index methods to GAO price comparisons			
	GAO full sample products @ GAO prices	GAO-IMS matched products @ GAO prices	GAO-IMS matched products @ IMS prices	GAO-IMS matched molecules @ IMS prices
<i>Canada-US price comparison using GAO list of drugs</i>				
Mean of US price/mean of Canada price	1.337	1.313	1.106	1.260
Mean of price relatives (Canada = reference)	1.766	1.766	1.661	1.668
Mean of price relatives (US = reference)	0.746	0.770	0.812	0.831
Median of price relatives (Canada = reference)	1.433	1.355	1.282	1.289
Median of price relatives (US = reference)	0.698	0.738	0.781	0.776
Laspeyres price index (US = reference)	-	-	0.791	0.753
Paasche price index (US = reference)	-	-	0.768	0.717
Paasche price index (CA = reference)	-	-	1.263	1.327
r_{xy}	-	-	-0.060	-0.131
v_x	-	-	0.388	0.498
v_y	-	-	1.277	0.729
N	121	85	88	77
<i>UK-US price comparison using GAO list of drugs</i>				
Mean of US price/mean of UK price	1.915	1.728	1.367	1.281
Mean of price relatives (UK = reference)	3.462	2.750	2.266	1.943
Mean of price relatives (US = reference)	0.552	0.583	0.738	0.841
Median of price relatives (UK = reference)	2.436	2.218	1.906	1.669
Median of price relatives (US = reference)	0.411	0.452	0.525	0.600
Laspeyres price index (US = reference)	-	-	0.698	0.740
Paasche price index (US = reference)	-	-	0.616	0.642
Paasche price index (UK = reference)	1.600 ^b	-	1.433	1.352
r_{xy}	-	-	-0.113	-0.165
v_x	-	-	0.851	0.818
v_y	-	-	1.227	0.980
N	77	56	57	56
				377

^aAdjusted for population.

^bReported in GAO Reports.

expensive than the US based on price per SU, but 19.3% more expensive based on price per KG, because more pills are required to yield a given total grams.

3.1.2. Quantity indexes

The quantity indexes in Table 1 are normalized by relative population size, so they can be interpreted as differences in quantity per capita. The Laspeyres SU indexes imply higher foreign consumption than the US for all countries except the UK — for example, France has quantity indexes more than twice the US level — whereas, Paasche indexes show other countries with lower per capita volume than the US, except France, which is at least 31% higher by all measures. Just as our price indexes show smaller cross-national differences than previously reported, so do our quantity indexes suggest smaller cross-national differences in per capita drug consumption.⁹ Moreover, differences in KG quantity indexes are generally smaller than differences in SU indexes, suggesting that systematic differences in strength per pill are partially offset by differences in number of pills per capita. However, since our indexes are based on the subset of matching molecules, they do not support firm conclusions about differences in total drug consumption. In particular, the molecules included here are a smaller fraction of total drug sales for Germany, France, Italy, and Japan than for the UK, the US, and Canada.

3.1.3. Paasche / Laspeyres ratios

The Paasche/Laspeyres ratios are identical for price and quantity indexes and are all less than one, consistent with a Gerschenkron effect.¹⁰ The P/L ratios for SU indexes range from 0.32 in Germany to 0.67 in the UK, whereas for KG indexes, the P/L ratios range from 0.41 in Japan to 0.78 in Canada. The generally lower P/L ratios for SU than for KG are consistent with the notion that systematic differences in strength per unit are partially offset by differences in number of units (more pills are consumed if strength per pill is low).

3.1.4. Global molecules

The price indexes for global molecules generally show slightly smaller price differences between countries than the indexes based on the larger, bilaterally matched samples. The Paasche/Laspeyres ratios are also generally (but not always) closer to unity for the global products than the bilateral products, suggesting less variation in consumption patterns for global drugs than for drugs that have less universal acceptance. Less cross-national price dispersion on global

⁹ For example, Burstall (1991) estimates per capita drug consumption by deflating total drug expenditures per capita by the Bureau European des Unions de Consommateurs (BEUC) (1989a,b) price indexes. This yields estimates of per capita volume, relative to the UK, of 3.06 for France, 2.06 for Italy and 1.53 for Germany, which are larger than most of the measures reported with our larger sample.

¹⁰ The choice of base country affects the magnitude but P/L ratios are always less than one.

products, particularly on price per SU, could reflect corporate strategies to maintain prices for global products within narrow bands in order to preempt parallel trade and/or regulatory cross-national spillovers; it could also reflect such regulatory spillover effects.¹¹

3.1.5. Comparison with U.S. General Accounting Office (1992, 1994)

Table 1c illustrates the contribution of sample vs. methods to the difference between our estimates and those in U.S. General Accounting Office (1992, 1994), to the extent possible with our data. The GAO US–Canada comparison (U.S. General Accounting Office, 1992) reported the ratio of US price to Canadian price for a market basket consisting of one pack for each of 121 branded products; median price relatives were also reported. The GAO US–UK comparison (U.S. General Accounting Office, 1994) used one pack for each of 77 products and reported a Paasche index for the UK, that is, US weights applied to US/UK price relatives, which is the reciprocal of the Laspeyres index with US as base. We are not able to replicate perfectly the GAO analysis because of the GAO's sample of 121 drugs for Canada, we have data on only 85; of the GAO's 77 drugs for the UK, we have data on 56.¹² Our measure of price is a weighted average price per standard unit for all forms/strengths/packs for each product, whereas the GAO US–Canada study used the price per pack and the GAO US–UK study used price per pill based on a single pack.

In Table 1c, column 2 reports the GAO's results based on their data and methods. In column 3, we attempt to replicate their results using IMS data for the subsample of drugs that we can match. For the US–Canada comparison, we can confirm that our subsample yields estimates similar to the full GAO sample for the GAO index measure: the ratio of US price for the market basket relative to Canadian price in row 1 (mean US price/mean Canada price) is 1.337 for their full sample of 121 products (column 2)¹³ and 1.313 for our subsample of 85 products (column 3). As a rough indicator of the effect of selecting a single pack, note that this unweighted mean US price/mean Canada price ratio falls from 1.31 to 1.106 when we substitute the IMS weighted average price per unit for all forms/strengths/packsizes (column 4) for GAO's single pack price (column 3). Column 5, which reports molecule level prices (weighted average over all

¹¹ Danzon (1997b) discusses manufacturers' incentives to reduce cross-national price differences in response to parallel trade and regulatory use of price comparisons.

¹² We attempted to match products in the IMS data to the GAO list, based on brand name and manufacturer. If the same manufacturer name could not be matched between the two countries, we substituted the same brand name product from a sole producer, if available. If this condition could not be met, the product is excluded from our sample.

¹³ We are unable to explain the difference between our estimate of 1.337 and the 1.32 reported in US General Accounting Office (1992).

products), shows that adding generics to the GAO sample of products has little effect. However, expanding the sample to include matching molecules (column 6) changes the Canada–US Laspeyres index from 0.75 for the GAO subsample to 1.02 for the full sample of molecules. Thus, the selection of leading branded products is one major source of the bias in the US–GAO comparison.¹⁴ Use of the ratio of unweighted mean prices adds a second major source of bias: for our full sample, the ratio of unweighted mean prices (mean US price/mean Canada price) is 1.61, whereas the Laspeyres index is only 1.02. The bias from using the mean of the price relatives is even larger and sign is indeterminate: mean price relative with Canada as base is 3.18, while mean price relative with US as base is 2.71!

For the UK, we cannot compute a UK-based Paasche index with our subsample of 57 products to compare to the GAO's index for their 77 product sample, because U.S. General Accounting Office (1994) does not report their weights. However, using the 57 GAO products and IMS average product prices and weights yields a UK-based Paasche index of 1.43, compared to 1.60 reported by GAO. Expanding the sample to include all matching molecules (column 6) reduces this index to 1.199, while the ratio of the unweighted means is 1.77. Again, the unweighted mean price relatives show sign reversal, with the US higher or lower than the UK, depending on the base.

Thus, the results for the UK, like those for Canada, show that both sample selection and using an unweighted index can each lead to bias of at least 20 percentage points; use of a single pack adds additional, smaller bias. The major source of sampling bias appears to be selection of leading branded products, not simply the exclusion of generics for those molecules that are multi-source. This is consistent with the finding of the U.S. General Accounting Office (1994) that substituting a generic, where available, for the branded product in their sample did not significantly affect their estimates. However, exclusion of generics would doubtless be a more significant factor for a comparison involving countries with very different generic shares, such as the US vs. France. The upward bias is exacerbated by use of unweighted means, which give undue weight to relatively high priced products. Comparisons based on unweighted price relatives (as in Minority Staff, 1998) are even more biased, extremely unstable and can reverse sign. This sign reversal results from the right-skew of the distributions of price relatives, which are bounded between zero and infinity, regardless of which country is the base.

¹⁴ This selection bias appears to result from the GAO's selection of products that are leaders in large therapeutic categories: relative to the full sample, the molecules in the GAO subsamples for both Canada and the UK have slightly more generics per molecule, fewer substitute molecules in the therapeutic category, are relatively early entrants and have broader global diffusion. The P/L ratios for the GAO subsample are also closer to one, with much smaller variation in price and quantity relatives.

3.1.6. Comparison with Bureau European des Unions de Consommateurs BEUC (1989a,b)

For their study of drug prices in the 12 member states of the European Economic Community (EEC), the Belgian Consumers' Association (Bureau European des Unions de Consommateurs BEUC, 1989a) drew a sample of the 25 leading prescription drugs, by sales value, in each state in 1987, to which they added any omitted drugs that were in the top 10 by volume (volume unit unspecified). Drugs were matched across countries if they were produced by the same manufacturers or were the sole source product. Generics were explicitly excluded on grounds that: (1) prices differ across generic forms within a country, and (2) single generic products are rarely in the top 25 in terms of sales. Thus, the notion of substitutability between generic equivalents was ignored. Prices were imputed if products were missing, which was common — only 78 of the sample of 125 products (62%) were available in nine or more of the 12 countries — and where form/packsize did not match across countries. Most of the analyses focus on retail prices. The one comparison of manufacturer prices (retail minus an average distribution percentage) reports an index of the unweighted average price for the market basket relative to the EEC-average of 100. Normalizing this index relative to its UK value (since the EEC average includes countries that are not in our sample) yields the following: France 0.58, Italy 0.74, Germany 1.127 (based on Bureau European des Unions de Consommateurs BEUC, 1989a, Table 10). Thus, based on this unweighted average applied to a sample of brand-only prices, the UK — a country with a relatively large generic share — appears relatively costly. By contrast, our Laspeyres SU weighted indexes applied to our sample of all matching molecules, including generics, show the UK as second cheapest.¹⁵ Bureau European des Unions de Consommateurs BEUC (1989b) extended this study to include the US, based on a sample of the 25 products for which they could find a perfect match. The retail price of this market basket of 25 products (unweighted and excluding VAT) showed the US at 1.28 of the UK index, compared to France 0.58, Italy 0.60, and Germany 1.24. These retail price indexes, which include distribution margins, are not strictly comparable to our manufacturer price indexes. Nevertheless, the general conclusion appears to hold, that comparisons that are based on an unweighted average of branded product prices only, excluding generics, tend to yield upward biased estimates of prices for relatively unregulated countries with large generic shares, notably the US, Germany and the UK, compared to France and Italy, which have strict price regulation and negligible generic shares.

¹⁵ Dividing each country's Laspeyres SU index by the UK Laspeyres SU index yields: France 0.81, Italy 1.04, Germany 1.495. These cannot be interpreted as UK-based Laspeyres indexes because the Laspeyres index is not transitive. The Paasche indexes are less comparable because each country's Paasche index incorporates different, country-specific weights, so differences in the indexes reflect volumes as well as price differences.

3.2. Decomposition of Paasche / Laspeyres ratios

The Bortkiewicz formula (Eq. 1) shows that the Paasche/Laspeyres differential can be decomposed into three components: the coefficient of correlation between price and quantity relatives r_{xy} and the coefficients of variation of price and quantity relatives (v_x and v_y), all measured relative to the respective Laspeyres index (see Eq. 1). These measures, which are invariant to population differences, are reported in Table 1. The hypothesis that the P/L differences primarily reflect a substitution effect towards products that are relatively cheap in each country implies that the correlation coefficients between price and quantity relatives, r_{xy} , should be negative and large. In our data, r_{xy} is indeed negative but the magnitudes are too small to “explain” the P/L differences — ranging from -0.001 for Japan to -0.106 for the UK in the bilaterally matched samples, and from -0.01 in Japan to -0.094 in Canada for the global sample.

By contrast, v_x and v_y are large and dominate the Paasche/Laspeyres differentials. The range of v_x is larger for KG (from 0.72 for Canada to 14.61 for Japan) than for SU (from 1.52 for Italy to 4.38 for Canada). This greater uniformity in price relatives per dose than per gram is consistent with the hypothesis that manufacturers and/or regulators tend to set price per dose within an affordable range. The v_y is generally larger for SU (from 5.69 in Japan to 129.72 in Canada) than for KG (from 2.87 in the UK to 77.21 in Japan), suggesting that differences in strength per pill are partly offset by differences in number of pills. v_x and v_y are generally smaller for global products than for the bilaterally matched sample, consistent with less variation in prices and quantities for global, “high consensus” products than for the lower consensus drugs in the bilateral samples.¹⁶

This evidence, that v_x and v_y dominate the P/L discrepancy for cross-national price comparisons of pharmaceuticals, and that r_{xy} is relatively small, is consistent with Jonas and Sardy’s (1972) findings for intertemporal quantity indexes for machinery in the US between 1889 and 1939. Like most previous studies, Jonas and Sardy (JS) focus on quantity indexes and attribute the P/L discrepancy to the process of industrialization, in which “the production of highly fabricated goods increases proportionately more than the production of slightly fabricated goods; and, at the same time, the relative prices of highly fabricated goods decrease”. This hypothesis obviously cannot explain our finding of similar patterns in cross-national comparison of pharmaceutical prices. However, the JS finding that the P/L ratio increased with the lag between the base and the comparison periods suggests the related hypothesis, that P/L ratios should be closer to unity in countries with similar medical norms, notably, the US, the UK, and Canada. This

¹⁶ For example, for the bilaterally matched molecules, five of the 12 values of v_y exceed 20 and three exceed 50, whereas for the global molecules only three of the 12 values of v_y exceed 20 and all but one are under 50.

assumes that use of a common language facilitates diffusion of medical research and consensus practices. Consistent with this, all four P/L ratios for global products for Canada and the UK are closer to unity than all but one of the eight ratios for the other countries.

Inspection of the data suggests that the high values for v_x and v_y partly reflect the extremely right-skewed distributions of both price and quantity relatives, which are bounded between zero and infinity. In our data, the distributions of price and quantity relatives pass tests for lognormality. Such departure from bivariate normality tends to bias Pearson correlation coefficients towards zero.¹⁷ As shown in Table 1c, an important implication of this extreme skewness of the price relative distributions is that price comparisons that are based on unweighted means of price relatives are extremely sensitive to the sample and choice of base.

4. Multivariate analysis of price and quantity relatives

4.1. Theory

Section 3 demonstrated that, in any two-country comparison, there is a significant dispersion in relative prices and quantities across molecules and this dispersion leads to large divergence between Laspeyres and Paasche indexes. In this section, we examine the contribution of various product and market characteristics to the dispersion of price relatives, using quasi-hedonic regression. Our equations are quasi-hedonic for three reasons. First, in the standard hedonic approach to estimating cross-area price indexes, the main focus is on the area indicator variables, which can be interpreted as area-specific bilateral price indexes relative to the omitted area, controlling for product characteristics that are assumed to differ randomly across areas while the implicit prices of these characteristics are assumed invariant (for example, Kokoski, 1991). However, in our cross-national comparison of drug prices, both product characteristics and their implicit prices are expected to differ systematically across countries, reflecting the incentives and constraints of each country's regulatory and reimbursement environment. Thus, cross-country differences in mean product characteristics and their implicit prices are of direct interest as factors that contribute to systematic, cross-country differences in drug prices. Our country intercepts reflect only unmeasured country-specific effects, conditional on measured characteristics.

¹⁷ The unweighted Pearson correlation coefficients between price and quantity relatives range from -0.006 for Canada/US to -0.07 for Italy/US. The same correlation coefficients for logged values are -0.55 and -0.35 , respectively. The distribution-independent Spearman rank correlation coefficients are -0.35 and -0.26 , respectively. Although these results with respect to extreme skewness pertain to the distribution of relative prices and quantities around zero, similar although less extreme patterns are found for distribution relative to the weighted mean, which is used in v_x and v_y .

Second, drug markets are imperfectly competitive because demand is influenced by such factors as insurance coverage, imperfect information, and physician prescribing, while supply is constrained by patents and regulation. Our quasi-hedonic regression coefficients are still implicit prices but cannot be interpreted as marginal values to consumers or marginal costs to producers.

Third, to capture the different impact of the imperfectly competitive market for pharmaceuticals in different countries, our price equations include measures of the extent of competition, although such measures would not belong in a pure hedonic equation. In countries that regulate prices, manufacturers and regulators presumably consider competitors prices in their negotiations over the regulated price. Moreover, since regulation sets a price ceiling but not a floor, price competition may still occur and is a hypothesis to be tested. Quality competition also occurs and may influence both unregulated and regulated prices. We therefore apply the same model to all countries, but test for cross-national differences in parameters.

The structural model, at the molecule level, is:¹⁸

$$P_{jkm} = P(\mathbf{Z}_{jkm}, G_{jk}, T_{jm}; R_j) \quad (2)$$

$$Q_{jkm} = Q(P_{jkm}, \mathbf{Z}'_{jkm}) \quad (3)$$

where P_{jkm} is the price of molecule k in therapeutic category m in country j , \mathbf{Z} is a vector of quality and market characteristics, \mathbf{Z}' is a subset of these characteristics, G_{jk} is the number of generic competitors in molecule k in country j , T_{jm} is the number of therapeutic substitute molecules in category m in country j , and R_j is the (unobserved) regulatory regime in country j . For the quantity Eq. (3), the vector \mathbf{Z}' includes only indicator variables for therapeutic category, to control for insurance and indication effects that may influence quantity directly. Thus, competition and most quality characteristics are not assumed to shift demand directly; rather, they influence quantity only indirectly through their effect on price.¹⁹

This simple model does not capture all relevant determinants of drug prices. First, demand in theory reflects incentives of patients, physicians and pharmacists. Our price measure is the manufacturer price, whereas the relevant price for patient demand is the patient's co-payment. In fact, in most countries in 1992, patient co-payments were low and often a fixed deductible per script, regardless of the product price (for example, in the UK, Germany), with total exemptions for the elderly, welfare recipients, etc. One exception is the US, where co-payments

¹⁸ Danzon and Chao (1999) provide a more detailed analysis at the individual product level.

¹⁹ Ellison et al. (1997) estimate a molecule-level demand system for four cephalosporins which includes own price and price of substitutes as the only explanatory variables. Price is treated as exogenous or instrumented by number of generic competitors, which is a restricted version of our model. Caves et al. (1991) report that aggregate molecule volume does not increase following generic entry, plausibly because a decline in promotion by originator firms offsets the effect of lower priced generics on volume.

varied from 0% to 100%, depending on health plan; overall, in 1992 roughly 50% of outpatient drug expenditure in the US was paid directly out-of-pocket (Levit et al., 1998). In 1992, physician incentives and constraints on drug choice were minimal, with few exceptions: fundholding physicians in the UK faced drug budgets; under reference pricing, German physicians had incentives to avoid products priced above the reference price, which applied primarily to multi-source products; and Japanese physicians were sensitive to the margin between the reimbursement and the acquisition cost (see below). Pharmacists did have incentives to be price sensitive in substituting between generically equivalent drugs in the US, the UK, and Canada. Since we lack data on these patient, physician, and pharmacy incentives for price-sensitivity, these unobserved characteristics might in theory influence both the unexplained country residuals and coefficients of some measured characteristics, as discussed below.

Second, manufacturer prices are regulated either directly or indirectly in all countries except in the US.²⁰ A rough categorization is that France, Italy, and Japan have strict price regulation, whereas Canada, Germany, and the UK have looser regulation. Specifically, France and Italy require approval of the manufacturer's price before a product becomes admitted for reimbursement. Subsequent price increases are rarely allowed and decreases may be mandated. In Japan, the manufacturer must obtain approval of the price for reimbursement at launch, and thereafter, the government sets the reimbursement price. However, since Japanese doctors dispense the drugs that they prescribe, drug manufacturers compete for market share by cutting actual price to increase the doctor's margin between reimbursement price and acquisition cost. The government revises downward the reimbursement prices every two (now one) years, based on surveys of manufacturer prices. In Canada, the Medicines Review Board monitors launch prices to assure that they are "reasonable", relative to foreign prices (for innovative products) or relative to existing product prices (for non-innovative products). Price increases are constrained to the general rate of inflation. Generic substitution is encouraged. The UK permits free pricing of new products, subject to the constraint that the rate of return from sales to the NHS on capital invested in the UK may not exceed a specified level; price increases require authorization. Reimbursement for multi-source, off-patent products is effectively a reference price system, where the Drug Tariff reimbursement price is based on supply prices of leading generics. Generic manufacturers compete by offering discounts off list prices, to increase the pharmacist's margin. The Drug Tariff price is periodically revised downward, but it reflects actual supply prices with a lag.²¹ Germany had free pricing until

²⁰ This description outlines the regulatory systems as of 1992, the year of our data, which predates more recent important changes in several countries (see Danzon, 1997a).

²¹ The NHS reimbursement to pharmacists includes a "clawback" (roughly 7%) which is intended to reflect the average discount below list prices.

1989, when reference pricing was introduced, focusing on multisource, off-patent products in Phase 1, extending to some therapeutic substitutes in Phases 2 and 3. Prices of non-reference priced products remained free until 1993. The expected effect of these regulatory characteristics on market attributes and coefficients is discussed below.

4.2. Variable definitions

4.2.1. Quality

Competition occurs on multiple dimensions of quality, and most regulatory systems take quality into account in setting prices. Hedonic regression would ideally include the characteristics that are of intrinsic value to consumers and regulators, in particular, therapeutic value and convenience. Since most of the relevant characteristics are not directly observable in our data, we include several proxy indicators for different dimensions of product quality.

A vector of binary indicators for one-digit therapeutic category (ATC1) controls for indication since, for example, cardiovascular drugs may, on the average, be more valuable than dermatologics. We use Global penetration, defined as the number of our seven countries in which the molecule is available, as a measure of therapeutic value. The implicit assumption is that, having incurred the fixed costs of drug development, a manufacturer will market a drug in any country in which its expected revenue exceeds the marginal cost of launch. Differences in Global penetration thus reflect differences in expected therapeutic value, assuming that expected revenue reflects expected value perceived by consumers and/or physicians and that the costs of launch are similar across products.²² Molecule Age (months from the first product launch in country j to September 1992) is an inverse indicator of relative therapeutic value, assuming that recent molecules are on the average more effective than older molecules.²³ In these cross-sectional data, Molecule Age may also reflect life-cycle effects due to regulation and other factors.

Other quality indicators measure characteristics of the formulation. Strength per unit is included as a control. The expected sign is positive if the within-molecule

²² Barral (1995) shows that global penetration is positively related to medical measures of therapeutic value. See also Thomas (1996) for a similar interpretation of this variable. Another, related interpretation is that products with high values of Global are products of multinational companies which may have economies of scale in diffusing products internationally, whereas products with low values of Global are more likely produced by smaller, local firms who may lack established connections in many countries but have political influence in regulated markets. These interpretations are related if multinational companies have higher hurdles for expected revenue in selecting the products that they take through development, compared to smaller companies.

²³ Molecule age is an inverse indicator of therapeutic value of a molecule, whereas individual product age is not expected to be related to therapeutic value because many new products are generic versions of old molecules.

effect (stronger products should be more effective, hence, receive higher prices) dominates the between-molecule effect (some very potent molecules have weak strength per pill but command high prices). The number of distinct formulation/strengths in the molecule (Form Codes) is an indicator of choice and convenience for patients, hence, is expected to be positively related to price.²⁴ Packsize (average number of units per pack) is expected to be inversely related to price per unit, if manufacturers pass on economies of scale in packaging. Since France, Italy, and Germany, have unit pack dispensing requirements, which prevent the pharmacist from splitting packs, average packsize is expected to be smaller, and competitive pressure to give volume discounts is expected to be lower in these countries than in the US, Canada, Japan, and the UK, where packsplitting is permitted and manufacturers offer large packs.

4.2.2. *Competition*

We include two measures of competition, recognizing that these are not product characteristics and hence, would not be appropriate for a pure hedonic regression under assumptions of competitive markets. Generic Competitors is the number of manufacturers of the molecule, including originators, licensees, parallel imports, and “true”, post-patent generic entrants. Therapeutic Substitute Molecules in the ATC3 is a measure of therapeutic competitors, that is, compounds that are chemically distinct but are used to treat the same indication.²⁵ Price is expected to be more negatively related to generic competitors than to therapeutic competitors, because generics are closer substitutes and because pharmacists have strong incentives to be price-sensitive in regimes that permit generic substitution. To test for first mover advantage, we include the lag in months between this molecule’s launch date and the launch of the first molecule in the ATC3 (molecule entry lag). The predicted sign is negative, if first mover advantage dominates product improvements that may be embodied in later molecules.

4.3. *Specification*

We use the log transform for prices and quantities, which are normally distributed after transformation. Log transforms of all explanatory variables are also used, since proportional effects are theoretically more plausible than linear

²⁴ Our variable is the maximum number of form/strengths for any manufacturer’s product in the molecule. This is a lower bound on the total number of different form/strengths for the molecule if different manufacturers produce different form/strengths.

²⁵ In the IMS ATC classification system, the first letter indicates body part (e.g., C for cardiovasculars), and successive digits indicate narrower definitions of indication, mode of action or substance. Our measure of therapeutic substitutes is imperfect, because not all compounds in an ATC3 are equally good substitutes and drugs in different ATC3s may sometimes be substitutes.

effects. We estimate a fully interacted model that pools all countries but permits intercepts and coefficients to differ across countries:

$$\ln P_{kj} = \beta \ln X_{kj} + \sum_{j=1}^6 \delta_{kj} D_j \ln X_{kj} + u_{kj} \tag{4}$$

where $j = 0, 1, \dots, 6$; $j = 0$ if country = US; $D_j = 1$ if country = j and $j > 0$; 0 otherwise. The dependent variable, $\ln P_{kj}$, is the log price per standard unit for molecule k in country j , X is a vector of country-specific characteristics for that molecule in country j . In this form, δ_j measures country-specific implicit prices, that is, the difference between parameter effects for country j and for the US. Thus, each country's net implicit prices for characteristics are:

US β
 UK $\beta + \delta_{UK}$
 Canada $\beta + \delta_{CN}$ etc.

This fully interacted model yields the same OLS coefficients as are obtained from separate regressions for each country. However, the pooled regression gives slightly different test statistics because the estimate of the residual variance σ_u^2 is based on the sum of squared residuals over all countries instead of being estimated separately for each country. The advantage of the pooled, interacted specification is that t -statistics for country interactions test directly for parameter differences across countries.

Table 2a reports results with the fully interacted model, which allows all parameters to differ across countries. Several of the coefficients are not significant at conventional levels, suggesting that the fully interacted model is too general and is not efficient. In Table 2b, we therefore report results from a constrained model that suppresses the interaction for those variables whose t -statistics in the fully interacted model were below unity. This imposes parameter equality for that variable in the comparison country and the US. The constraints improve efficiency but could impose bias if the constrained parameters are not truly identical. A test of the joint hypothesis, that the true value of the constrained parameters is zero, cannot be rejected, suggesting that any such bias is small.²⁶

4.4. Empirical results: price equations

The parameter estimates in Table 2b confirm most of the basic hypotheses about effects of quality and market characteristics on price, but with significant differences across countries.

²⁶ The F statistic for the joint hypothesis that the constrained interactions are equal to zero is 0.67.

Table 2

a. Regression results for pharmaceutical prices — 1992 fully interacted model (*t*-statistics in parentheses) log price per standard unit, for molecule/ATC matched with US

Variable	US	CN	GE	FR	IT	JP	UK
Intercept	3.301 (8.592)	1.010 (1.603)	1.120 (1.681)	1.458 (2.115)	1.670 (2.483)	4.367 (5.672)	0.450 (0.661)
<i>Quality</i>							
Strength (ln)	0.125 (6.435)	-0.036 (-1.093)	0.084 (2.631)	0.002 (0.057)	0.052 (1.561)	-0.046 (-1.342)	-0.009 (-0.251)
Age (ln)	-0.190 (-3.516)	-0.116 (-1.372)	-0.212 (-2.438)	-0.434 (-4.916)	-0.394 (-4.643)	-0.719 (-6.833)	-0.340 (-3.658)
Form codes (ln)	0.282 (3.927)	-0.085 (-0.684)	0.114 (0.987)	-0.165 (-1.314)	-0.068 (-0.545)	-0.058 (-0.445)	-0.159 (-1.280)
Global (ln)	0.458 (4.680)	-0.226 (-1.286)	-0.430 (-2.352)	-0.648 (-3.020)	-0.830 (-3.921)	-0.683 (-3.704)	-0.150 (-0.732)
Packsizes (ln)	-0.719 (-17.713)	-0.068 (-1.046)	0.170 (2.524)	0.027 (0.383)	0.032 (0.446)	0.029 (0.472)	0.126 (1.835)
<i>Competition</i>							
Generic competitors (ln)	-0.566 (-13.637)	0.110 (1.138)	0.188 (2.470)	0.629 (5.954)	0.770 (8.552)	0.693 (8.499)	0.329 (3.117)
Therapeutic substitute molecules (ln)	0.094 (1.389)	-0.103 (-0.910)	-0.314 (-3.109)	-0.233 (-2.086)	-0.193 (-1.877)	-0.128 (-1.237)	-0.247 (-2.272)
Therapeutic substitute molecule entry lag (ln)	-0.043 (-1.902)	0.017 (0.451)	0.084 (2.340)	0.050 (1.284)	0.039 (1.059)	0.057 (1.463)	0.063 (1.693)
<i>Therapeutic categories</i>							
A	-0.843 (-5.305)	0.209 (0.826)	0.195 (0.775)	0.796 (3.061)	0.810 (3.144)	0.648 (2.480)	0.390 (1.537)
B	-0.473 (-1.776)	0.332 (0.811)	0.440 (1.092)	0.725 (1.785)	0.699 (1.757)	0.555 (1.346)	0.351 (0.824)
D	-0.962 (-5.793)	0.133 (0.497)	0.442 (1.692)	0.689 (2.547)	0.924 (3.331)	-0.183 (-0.669)	0.356 (1.345)
G	0.345 (1.636)	-0.482 (-1.422)	-0.706 (-2.233)	0.028 (0.083)	-0.015 (-0.046)	-0.399 (-1.134)	-0.264 (-0.798)
H	-0.257 (-0.897)	-0.264 (-0.610)	0.616 (1.452)	0.676 (1.509)	0.296 (0.687)	0.298 (0.686)	0.243 (0.507)
J	0.625 (3.529)	-0.514 (-1.767)	-0.082 (-0.285)	-0.465 (-1.559)	0.032 (0.111)	-0.217 (-0.759)	0.155 (0.531)
L	0.727 (2.931)	-0.230 (-0.578)	0.407 (1.100)	-0.017 (-0.045)	0.077 (0.207)	0.375 (0.819)	0.034 (0.082)
M	-0.010 (-0.051)	0.166 (0.525)	-0.546 (-1.784)	-0.159 (-0.482)	-0.101 (-0.312)	-0.327 (-1.006)	0.292 (0.916)
N	0.193 (1.281)	-0.445 (-1.884)	-0.633 (-2.728)	-0.469 (-1.912)	-0.261 (-1.081)	-0.528 (-2.148)	-0.314 (-1.329)
P	-0.012 (-0.035)	-0.694 (-1.247)	-0.736 (-1.411)	-0.374 (-0.673)	-0.491 (-0.826)	-1.535 (-1.413)	-1.262 (-2.445)
R	-0.321 (-1.659)	-0.126 (-0.415)	0.029 (0.095)	0.374 (1.182)	0.424 (1.329)	0.238 (0.766)	0.307 (1.010)
S	-2.234 (-9.698)	-0.600 (-1.629)	-0.305 (-0.823)	0.140 (0.372)	0.533 (1.384)	0.222 (0.558)	0.026 (0.058)

N = 2.987

Adjusted R² = 0.620

b. Regression results for pharmaceutical prices — 1992 constrained model (*t*-statistics in parentheses) log price per standard unit, for molecule/ATC matched with US

Variable	US	CN	GE	FR	IT	JP	UK
Intercept	3.260 (10.334)	1.203 (2.428)	1.008 (1.769)	1.601 (2.726)	1.743 (3.203)	4.197 (6.266)	0.389 (0.742)
<i>Quality</i>							
Strength (ln)	0.124 (9.597)	-0.022 (-0.798)	0.089 (3.766)	-	0.052 (1.924)	-0.066 (-2.542)	-
Age (ln)	-0.184 (-3.660)	-0.150 (-2.056)	-0.216 (-2.665)	-0.443 (-5.219)	-0.387 (-4.863)	-0.690 (-6.906)	-0.354 (-3.953)
Form codes (ln)	0.273 (6.778)	-	-	-0.170 (-1.558)	-	-	-0.145 (-1.451)
Global (ln)	0.430 (5.163)	-0.241 (-1.493)	-0.341 (-2.016)	-0.645 (-3.170)	-0.820 (-4.102)	-0.617 (-3.589)	-
Packsize (ln)	-0.705 (-29.931)	-0.088 (-1.609)	0.180 (3.358)	-	-	-	0.106 (1.898)
<i>Competition</i>							
Generic competitors (ln)	-0.567 (-14.804)	0.097 (1.110)	0.231 (3.391)	0.645 (6.369)	0.756 (9.049)	0.674 (9.100)	0.322 (3.188)
Therapeutic substitute molecules (ln)	0.069 (1.326)	-	-0.279 (-3.118)	-0.216 (-2.189)	-0.188 (-2.135)	-0.144 (-1.616)	-0.200 (-2.137)
Therapeutic substitute molecule entry lag (ln)	-0.037 (-2.097)	-	0.074 (2.286)	0.041 (1.157)	0.037 (1.110)	0.057 (1.591)	0.056 (1.617)
<i>Therapeutic categories</i>							
A	-0.736 (-7.887)	-	-	0.704 (3.719)	0.694 (3.792)	0.572 (3.025)	0.237 (1.305)
B	-0.293 (-1.773)	-	0.272 (0.851)	0.555 (1.744)	0.510 (1.637)	0.403 (1.216)	-
D	-0.965 (-9.617)	-	0.486 (2.562)	0.704 (3.443)	0.910 (4.258)	-	0.316 (1.603)
G	0.275 (2.423)	-0.361 (-1.481)	-0.609 (-2.674)	-	-	-0.348 (-1.314)	-
H	-0.179 (-1.265)	-	0.593 (1.851)	0.600 (1.743)	-	-	-
J	0.611 (6.754)	-0.530 (-2.626)	-	-0.445 (-2.211)	-	-	-
L	0.742 (6.184)	-	0.436 (1.617)	-	-	-	-
M	0.021 (0.205)	-	-0.579 (-2.607)	-	-	-0.292 (-1.184)	-
N	0.216 (1.794)	-0.535 (-3.165)	-0.623 (-3.470)	-0.468 (-2.366)	-0.304 (-1.595)	-0.550 (-2.910)	-0.401 (-2.093)
P	-0.234 (-1.027)	-0.448 (-0.954)	-0.474 (-1.109)	-	-	-1.377 (-1.334)	-1.077 (-2.535)
R	-0.290 (-2.738)	-	-	0.351 (1.449)	0.389 (1.575)	-	0.237 (1.037)
S	-2.230 (-17.798)	-0.564 (-2.064)	-	-	0.482 (1.597)	-	-
N = 2.987							
Adjusted R ² = 0.622							

(continued on next page)

4.4.1. *Quality*

Price is inversely related to molecule age, consistent with the hypothesis that newer molecules offer improved therapeutic quality. The Age coefficient measures a pure age effect, controlling for number of generic and therapeutic competitors that increases with age. The molecule-age elasticity for the US is -0.18 , with significant negative interactions for all countries that imply age elasticities ranging from -0.33 for Canada to -0.87 for Japan. The ranking of elasticities — more negative for France, Italy, and the UK than for Germany and Canada — is consistent with the fact that regulatory systems in the first three countries do not permit post-launch inflation adjustments, such that real prices fall over the life of the molecule, whereas, Canada permits a CPI increase. For Germany, declining prices over the life-cycle is consistent with other evidence (Danzon and Kim, 1996a,b) and may reflect spillover effects from other countries and/or the reference price system introduced in 1989, which initially targeted older molecules. The extreme negative age effects in Japan reflect the interaction between competition and regulation, and are consistent with other empirical evidence (Danzon and Kim, 1996a,b; Ikegami et al., 1998).

The elasticity of price with respect to Global penetration is 0.43 in the US, consistent with the joint hypothesis that global diffusion is an indicator of therapeutic value and that more effective drugs obtain higher prices in unregulated markets. The Global interactions are insignificant or small for other less regulated markets (UK, Canada, and Germany), but significantly negative for the strictly regulated countries. The net effect (US coefficient plus country-specific interaction) implies a negative price elasticity with respect to the therapeutic value (Global) for France (-0.22), Italy (-0.39), and Japan (-0.19).

Price is increasing in Strength per standard unit, as expected. The interaction is significantly negative for Japan, where the practice of polypharmacy may reduce the value of strong pills. Price is also positively related to the number of Forms available for the molecule, as expected, if range of formulations enhances convenience, effectiveness, and value. These effects do not differ significantly across countries. Price decreases with packsize, consistent with economies of scale in packaging that are (at least partially) passed on to purchasers.²⁷ Several of the 12 ATC1 category dummies are significant for the US, implying significant differences in the mean prices for different indications, relative to the omitted cardiovascular category, possibly due to differences in therapeutic value and/or average insurance coverage across therapeutic categories. Many country-interactions for

²⁷ The positive interaction for Germany may reflect the co-payment structure of a flat fee per script (DM3, except 0 for reference priced drugs), which created incentives for patients to prefer larger packs per prescription. In 1993, co-payments were related to the price of the drug; and in 1994, this co-payment schedule was based on packsize. For effects of packsize at the product level see Danzon and Chao (1999).

ATC1s are significant, implying that countries differ in medical norms and insurance for different types of drugs.

4.4.2. Competition

The US elasticity of molecule price with respect to Generic Competitors is -0.57 , consistent with other evidence of generic competition in the US (Grabowski and Vernon, 1992; Ellison et al, 1997). The positive interactions imply that generic competition has a weaker but still negative net effect on molecule price in the less regulated markets: Canada (insignificantly different from the US), Germany (-0.34), and the UK (-0.25). However, the net effect of generics on molecule price is positive for France (0.08), Italy (0.19), and Japan (0.11). These positive elasticities are consistent with anecdotal evidence that multi-source suppliers in these countries are usually licensed co-marketers rather than competing generic manufacturers or minor “new” products that enter to obtain a higher regulated price.²⁸ Our estimates of the effects of generic competition on price may be subject to endogeneity bias, if generics entry is related to expected prices and expected prices are correlated with actual prices. In that case, our estimates are a lower bound for the competitive effects of generics on price.

Competition from therapeutic substitute molecules appears to have no significant effect on price in the US and Canada.²⁹ However, these list price data for the US do not reflect discounts given directly to manage care customers to gain preferred formulary status. Such competitive discounting is likely to be greatest in crowded therapeutic categories, leading us to underestimate the extent of therapeutic competition. Further downward bias is likely due to our inability to control for promotional expense and possible endogeneity of number of molecules in a class.³⁰ Number of therapeutic substitute molecules appears to have small but significant negative effects on price in France, Italy, Germany, and the UK, but the interpretation is unclear. Since France and Italy show no evidence of competitive effects of generics, which are closer substitutes, the most plausible explanation of the negative Therapeutic Substitute coefficients is that regulators use a form of implicit reference pricing, setting prices for new products based on prices of established products. The prices of these established products are inversely related to age because of regulatory constraints on inflation adjustments, as shown earlier.

²⁸ We follow IMS (and the manufacturer) in defining a new form — for example, a delayed release tablet — as a new product rather than a new form of an old product if it has a different product name. Thus Procardia XL is a distinct product from Procardia.

²⁹ Ellison et al. (1997) find fairly high cross-price elasticities between generic substitutes, smaller but sometimes significant elasticities between therapeutic substitutes in their study of cephalosporins in 1985–1991.

³⁰ If promotion has spillover effects that expands demand for the class, omitting a control for promotion would lead us to underestimate the effects of therapeutic substitutes on price. Similar bias may result if entry is positively related to expected prices which are positively correlated with observed prices.

Thus, this implicit price setting mechanism would result in the observed inverse relation between price and number of molecules in the class. For Germany and the UK, the negative Therapeutic Substitute coefficients findings may reflect competition or spillover effects of regulation from France and Italy, if parallel trade and international comparisons constrain price divergence across EU countries.

For the US and Canada, the significant negative Therapeutic Substitute Entry Lag coefficient implies that successive molecules enter at lower prices, with a 3.7% per month price reduction for each month of entry lag after the first molecule in a class.³¹ This indicates competitive pricing by successive entrants that does not fully erode the first mover advantage. Other country interactions are generally positive, but significant only for Germany. Since the coefficients of number of therapeutic substitutes and therapeutic entry lag tend to be offsetting, the net effects of therapeutic substitutes depend on the combined effect, as discussed in Section 5.

4.4.3. *Quantity equations*

Table 2c reports price elasticities from the second stage of two-stage least squares estimates of the structural quantity equation (Eq. 3), which includes only ATC1 dummies in addition to (endogenous) price, with full interaction. All the right-hand-side variables in Eq. 4 (i.e., the variables in Table 2a) are used as instruments for price in the first stage. The price elasticity for the US is -1.29 , with no significant difference for Canada or Germany. Elasticities are still negative but significantly smaller in absolute value in the UK (-0.91), Japan (-0.76), France (-0.67), and Italy (-0.36). These significant negative elasticities in the logs imply that the very low correlations between absolute prices and quantities in Table 1 are due to extreme values rather than to lack of an overall inverse relationship.

Our elasticity estimates are larger (in absolute value) than most prior estimates, and several factors may contribute. First, several previous studies (for example, Leibowitz et al., 1985) are based on aggregate expenditures, and hence, are expected to show less elastic demand than our measures, which reflect between-molecule substitution. Second, most prior studies estimate demand response to out-of-pocket price to consumers, whereas our manufacturer level prices are only roughly proportional to consumer prices, depending on proportionality of distribution margins, taxes and co-payment rates. Proportionality is most plausible for the US at this time and for some consumers in Canada, but not for the other countries. Thus, if price sensitivity were driven solely by consumer co-payments, we might expect small or zero quantity elasticities with respect to these manufacturer prices.

³¹ Similarly, Boston Consulting Group (BCG) (1993) reports that late entrants enter at a price discount relative to the market leader, and that these discounts are greater in more crowded therapeutic categories.

Third, however, to the extent that demand decisions also reflect physician incentives, through indicative drug budgets, prescription monitoring by third party payers, etc., the full price is the relevant measure, not the consumer's co-payment. Fourth, to the extent that regulatory systems require price reductions if volume exceeds target levels, this imposes a spurious inverse relation between quantity and price that would bias up (in absolute value) the estimated price elasticity in countries with regulation.³² Sorting out the contribution of these factors to the observed elasticities with respect to manufacturer price is an important topic for future research.

5. Accounting for price differentials: characteristics vs. parameters

We have shown that the relation between prices and product characteristics differs significantly across countries. In this section, we use the regression results in Table 2b to examine how far differences in mean values of these characteristics and their parameter effects can account for the (log) mean foreign/US price ratio. The (log) mean price relative for country j relative to the US can be written:

$$\ln R = \ln(P_j/P_u) = \ln P_j - \ln P_u = \ln X_j \beta_j - \ln X_u \beta_u + u_j - u_u \quad (5)$$

Comparing Eqs. (4) and (5):

$$\begin{aligned} \beta &= \beta_u \\ \delta_j &= \beta_j - \beta_u \end{aligned}$$

or

$$\beta_j = \beta_u + \delta_j$$

Eq. (5) can thus be rewritten:

$$\ln R = (\ln X_j - \ln X_u) \beta_u + \ln X_j \delta_j$$

The mean price ratio can thus be decomposed into two components. The first component or characteristics effect $(\ln X_j - \ln X_u) \beta_u$ reflects the difference in mean characteristics of our sample of drugs in country j , relative to the US, evaluated at US parameter values. The second component, $\ln X_j (\beta_j - \beta_u) = \ln X_j \delta_j$, is the country interaction or implicit price effect, which reflects the difference in implicit prices for characteristics in country j , compared to the US.³³ The country intercept estimates (with opposite sign) the unexplained country residual effects that are not explained by measured characteristics or their parameter effects. It also subsumes country effects for the omitted cardiovascular

³² France applied a total revenue constraint "envelope globale" to certain products. The UK PPRS profit constraint implies a portfolio revenue constraint, given the capital base. For Italy (the Emilia Romagna region) for 1989–1993, Anessi (1997) estimates own price elasticities for individual cardiovascular products with respect to out-of-pocket prices to be -0.26 to -0.36 .

³³ For application of a similar decomposition to wage differences, see Oaxaca (1973), Smith and Welch (1977), and Reimers (1983).

category. Cross-country differences in implicit prices for product characteristics are of interest, although in this pharmaceutical context, the standard interpretation of hedonic equations under assumptions of competitive equilibrium does not strictly apply. In an industry with significant fixed costs and imperfect competition, unregulated prices should approximate consumer valuations, rather than marginal costs. However, imperfect information and insurance may undermine this interpretation for pharmaceuticals and other medical services. In addition, in countries with regulation, monopsony government purchasers may drive prices towards marginal cost. The implicit characteristic prices presumably reflect the net effect of all these factors. Table 3 shows that differences in implicit prices are relatively more important than differences in mean product characteristics in accounting for mean price differences, at least for these matching products.

5.1. *Quality*

The main factors that tend to reduce drug prices in most other countries relative to the US are more negative returns to molecule age and to therapeutic value, as measured by global penetration. Returns to age and global penetration are most negative in France, Italy and Japan, which have the strictest price regulation (Table 3, column 7, “parameter interactions”). Smaller but still negative age and global effects contribute to lower prices in Germany and Canada; only age effects are significant for the UK.³⁴ Smaller packs due to unit pack dispensing contribute to higher prices in other countries. But the overall effect of the quality variables (strength, age, forms, global, and packsize), including characteristics and parameter values, is to reduce prices significantly in the strictly regulated markets compared to the US, and to a lesser extent, the UK, Germany, and Canada. Differences in therapeutic mix (ATC1 dummies) and their parameter effects contribute very little to the overall mean price differences for these matching molecules, but this conclusion cannot necessarily be generalized to the full universe of drugs in each country.

5.2. *Competition*

The price-reducing effects of generic competition partially but not completely offset the more negative effects of age and global in the regulated countries. All other countries have fewer generic competitors per molecule than the US, and the price competitive effect of a given number of generic competitors is weaker

³⁴ The higher mean globalization score for foreign countries than for the US is an artifact of the bilaterally matched sample. Each non-US sample includes only drugs that are also available in the US, whereas the US sample includes all drugs that are available in at least one foreign country, and is therefore a larger sample. Other analysis (not reported here) shows that the fraction of sales that is attributable to global drugs is higher in the US than in France, Italy, Germany or Japan.

France vs. US							
Variable	US mean	FR mean	US parameter	FR parameter	Characteristic effects	Parameter interactions	Total
Strength	-3.1947	-3.3296	0.1242		-0.0168		-0.0168
Age of molecule	5.1501	5.2840	-0.1835	-0.4429	-0.0246	-2.3402	-2.3648
Forms	0.7942	0.5656	0.2729	-0.1704	-0.0624	-0.0964	-0.1587
Global	1.4675	1.7235	0.4297	-0.6449	0.1100	-1.1115	-1.0015
Packsizes	4.2203	3.2359	-0.7052		0.6942		0.6942
Quality subtotal					0.7005	-3.5481	-2.8476
Generic competitors	1.0400	0.4293	-0.5674	0.6450	0.3466	0.2769	0.6234
Therapeutic substitute molecules	1.9829	2.1812	0.0693	-0.2157	0.0137	-0.4706	-0.4568
Therapeutic molecule entry lag	3.9194	4.2098	-0.0367	0.0413	-0.0107	0.1739	0.1632
Competition subtotal					0.3496	-0.0198	0.3298
Therapeutic categories subtotal					0.0352	0.1050	0.1402
Residual subtotal	1.0000	1.0000	3.2600	1.6015	0.0000	1.6015	1.6015
Total: log of observed price ratios							-0.7761
Italy vs. US							
Variable	US mean	IT mean	US parameter	IT parameter	Characteristic effects	Parameter interactions	Total
Strength	-3.1947	-3.2587	0.1242	0.0520	-0.0079	-0.1694	-0.1774
Age of molecule	5.1501	5.2171	-0.1835	-0.3871	-0.0123	-2.0197	-2.0320
Forms	0.7942	0.6336	0.2729		-0.0438		-0.0438
Global	1.4675	1.7256	0.4297	-0.8203	0.1109	-1.4155	-1.3046
Packsizes	4.2203	3.1055	-0.7052		0.7861		0.7861
Quality subtotal					0.8330	-3.6046	-2.7716
Generic competitors	1.0400	0.5657	-0.5674	0.7562	0.2692	0.4277	0.6969
Therapeutic substitute molecules	1.9829	2.2460	0.0693	-0.1876	0.0182	-0.4213	-0.4031
Therapeutic molecule entry lag	3.9194	4.1805	-0.0367	0.0367	-0.0096	0.1536	0.1440
Competition subtotal					0.2778	0.1600	0.4378
Therapeutic categories subtotal					0.0862	0.1814	0.2677
Residual subtotal	1.0000	1.0000	3.2600	1.7429	0.0000	1.7429	1.7429
Total: log of observed price ratios							-0.3232

(continued on next page)

(except for Canada). However, the overall price-increasing effect of generic competition (i.e., the effect of fewer generics plus the effect of weaker price competition among generics in non-US countries) ranges from 0.62 in France to 0.70 in Italy, which is much smaller in magnitude than the negative molecule age effect (from -2.03 in Italy to -3.76 in Japan) or the negative global effect (from -0.94 in Japan to -1.30 in Italy). Note that these characteristics are related: incentives for generic entry are weak where demand is not price sensitive and where regulated originator prices decline with molecule age, hence, are very low by the time of patent expiry. The combined effect of therapeutic substitute molecules and therapeutic substitute entry lag contributes little to explaining the magnitude of cross-national price differences, although in general the combined effect is to reduce prices in other countries relative to the US (insignificant difference for Canada). As discussed earlier, this effect is more plausibly attributed to regulation than to competition, at least for France, Italy and Japan.

5.3. *Unmeasured effects*

The country intercepts can be interpreted as conditional estimates of country price differentials, controlling for measured characteristics and their implicit prices that are themselves influenced by regulation. These country intercepts are positive and significant in all countries except the UK. This implies that predicted values based solely on measured characteristics are below actual values, but that this is partially offset by positive, country-specific effects due to unmeasured factors, such as insurance. As an alternative, unconditional measure, Table 2d reports the country intercepts for (a) the full specification in Table 2a; (b) omitting the competition variables; and (c) omitting molecule age and competition variables, which appear to be the characteristics that are most affected by regulation. When competition alone is omitted, all the country interactions are insignificant except Japan, which is still positive. When molecule age is also omitted, the country interactions for Germany, France, and the UK, are significantly negative, while Canada, Italy, and Japan are not significantly different from the US.

Thus, the country intercepts from quasi-hedonic regression for drug prices, which in theory, might offer an approach to measuring cross-national price differences that controls for product differences, are in fact extremely sensitive to specification. For some countries, these measures differ in both magnitude and sign from the Laspeyres and Paasche indexes in Table 1. This is a further evidence of the sensitivity of drug price comparisons to methods used. Improving these estimates from hedonic regression is the subject of ongoing research.

6. Conclusions

We have demonstrated that the conventional view, that drug prices are much higher in the US than in other countries, is biased due to the small, unrepresenta-

tive samples and inappropriate methods used in prior studies. Indexes based on a comprehensive sample that include generics show smaller cross-national differences in the average cost of drug therapy, at manufacturer prices, than implied by previous studies. However, this analysis has also demonstrated the sensitivity of cross-national price comparisons to the methods used, including sample selection, weights, unit of measure, and index. Laspeyres indexes consistently exceed Paasche indexes, by up to 50 percentage points in some cases. These differences reflect in part the right-skewed distributions of price and quantity relatives for each bilateral comparison. Although specific magnitudes would change if a country other than the US were used as the base, the Paasche/Laspeyres divergence remains, due to dispersion of relative prices and quantity across products.

The dispersion of relative prices across products in any bilateral comparison reflects both differences in product characteristics for the matching molecules and differences in market characteristics, particularly the extent of competition between generic equivalents. Differences in mean characteristics are generally less important than differences in implicit prices for these characteristics. The main factors tending to lower prices in other countries, relative to the US, are lower prices for older molecules and for therapeutic value, as measured by global penetration. These negative returns to age and therapeutic value are particularly strong in the countries with strict price regulation — France, Italy and Japan — and are consistent with the structure of their regulatory systems. On the other hand, generic competition is more effective at lowering prices in the US and in the less stringently regulated markets (Canada, Germany, and the UK) than the more regulated markets (France, Italy, and Japan). Demand elasticities estimated from regression analysis are significantly negative for all countries, but are more negative in the US and the other less regulated countries than for the strictly regulated countries.

The main conclusion from this analysis is that any generalizations about relative prices for drugs in different countries are tentative at best, because of the diversity of products, prices, and volumes, which makes conclusions very sensitive to the sample and methods. The safe conclusion is that results will be systematically biased if the comparison is based on a sample that is unrepresentative with respect to either age of molecules, extent of globalization or generic share. Much remains unexplained about the factors that contribute to cross-national price differences. Although we have identified certain factors — returns to age, therapeutic merit, and competition — nevertheless, controlling for these measured factors leaves large unmeasured country effects. The contribution of insurance structure and other factors to these unexplained differences is an important subject for future research.

This analysis also has implications for the use of international price comparisons to regulate domestic prices. The conclusions depend on the objectives, but in any case, there are no simple answers. One possible objective of such external referencing is to achieve an average domestic price level that is comparable to the

average price level in the comparison countries. This objective will not be achieved by comparing prices of individual new branded products at launch, on a product-by-product basis, because post-launch price paths diverge due to country-specific regulatory and competitive environments. A theoretically more appropriate comparison would use the discounted present value of expected prices over the molecule life-cycle. Most countries with external referencing use as their benchmark the unweighted median, mean, or minimum price in the market basket drawn from the comparison countries. We have shown that such unweighted measures are extremely sensitive to the sample selected, particularly if the comparison is based on a single pack of a single manufacturer. However, although weighting would in theory, reduce the instability, there are no obvious appropriate weights for such multilateral comparisons of prices of a single product. If different countries apply external referencing to the same products, but use different benchmark countries or different weights, then, each country's perspective on the same distribution of relative prices will yield a different conclusion about their relative price level.

A second possible regulatory objective is to set price differences across countries to achieve appropriate per capita contributions to the joint costs of pharmaceutical R&D, based on Ramsey pricing principles (Danzon, 1997b). For this objective, the appropriate comparison is the discounted present value of expected revenue per capita over the originator product's life-cycle, which takes into account cross-national differences in per capita quantity as well as price over the life-cycle, for example, due to different post-patent generic penetration rates across countries.³⁵ Further research is necessary on both theory and practical empirical measures, if international comparisons are to be used to achieve the desired price levels for consumers and returns for manufacturers.

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³⁵ Danzon and Kim (1996a,b).

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