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An Exploratory Analysis of Pharmaceutical Price Disparities and Their Implications Among Six Developed Nations

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Working Paper 06-07
April 2006

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Executive Summary

In our study of 43 drugs, prescription drug prices in several wealthy nations (Australia, Canada, France, Germany, and the U.K.) were much lower than in the U.S. on average, well below relative per capita GDP. There was relatively little difference among the five foreign nations. All this is consistent with previous research. After separating less-unique from more-unique drugs, however, important new findings emerged. Relative prices for less-unique drugs, which are subject to strong competition, were at about half the U.S. level. We suggest that this reflects the exercise of monopsony power that does not exist in the U.S., where buyers as well as sellers compete. On the other hand, relative prices for highly unique drugs tended to be approximately proportional to per capita GDP or higher. Remarkably, biotech drugs were priced at or above U.S. levels in Canada and France.

These results carry uneasy implications for the future of pharmaceutical research. The follow-on drugs that make therapeutic classes competitive also amplify the incentives to conduct new R&D within these classes even as R&D incentives for pioneer brands disappear with the approach of patent expiration. Our results suggest that price controls operate to blunt these incentives for follow-on drug research, leaving most of the burden to U.S. purchasers. Because these follow-on R&D results are often extremely valuable, the implications merit substantial concern.

In contrast, biotech drug prices in foreign nations appear to be above profit-maximizing levels, which we suggest is caused by political forces in the U.S., while foreign revenues, as one would expect, are very low. This, too, undermines research incentives, especially for creating highly innovative drugs.

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1. Why International Pharmaceutical Prices Matter

Pharmaceuticals play a large and increasing role in health care and the prevention of illness. Technological advances have accelerated the pace of basic research and vastly expanded the scope of drug development. While government and non-profit organizations conduct the bulk of basic research, for-profit firms discover many potential drugs and almost always conduct the extraordinarily expensive clinical trials necessary to eliminate products that are dangerous or ineffective and bring successful drugs to market.[1] The possibility of making profits from the sale of newly approved drugs provides the motivation to invest in drug development. Those profits must, on average, cover development costs plus compensation for the large financial risks involved in an enterprise in which the great majority of promising new treatments never reach the market.

Pharmaceuticals comprise an international market in which technology disperses rapidly as nations avail themselves of the health benefits of new drugs. Developed economies and, to an increasing extent, mid-level economies such as Brazil, comprise the primary markets from which profits can be made and development costs recouped. Although the United States is by far the largest economy in the world, the ability to realize profits from other wealthy nations forms a substantial part of the incentives for drug development. International pharmaceutical pricing therefore plays a crucial role in drug development.

Pharmaceutical R&D is lengthy and expensive, consuming an average of approximately one billion $US over perhaps ten years of research (DiMasi, Hansen, and Grabowski 2003). A substantial portion of pharmaceutical costs are sunk costs, i.e., costs that are incurred before a new drug enters the market. Because drug prices are set according to market demand (rather

[1] DiMasi, Hansen, and Grabowski (2003) reviewed comprehensive drug development data bases. They found that of the 284 drugs approved in the United States during 1990-1999, government sources accounted for 3.2% and academia, 3.5%, with the other 93.3% coming from private industry. Reichert and Milne (2002) explored in more detail the relationships between public and private research, noting among other things the very limited extent to which NIH engages in the kinds of clinical trials necessary to demonstrate safety and efficacy of new drugs. A 2001 NIH report examined the genesis of 47 FDA-approved drugs with at least $500,000 in U.S. sales in 1999, finding that only four involved direct or indirect federal patents (NIH 2001).

than simply to recover costs, which only occurs on average over time (cf. Danzon 1998, p. 296-298), successful drugs are priced far above the marginal costs of production and distribution. Up-front sunk costs have been estimated to comprise some 70% of pharmaceutical costs, with manufacturing and other short-run costs accounting for only about 30% (Danzon 1998, p. 296). This provides the opportunity for differential pricing. Economic theory predicts that profit-maximizing firms with large sunk costs will charge higher prices in markets with stronger demand (i.e., markets with lower price elasticities), an approach that roughly accords with the theoretical model of Ramsey pricing (Danzon and Towse 2003; ITA 2004, p. 16; Ramsey 1927).

Pharmaceutical prices within the U.S. and among developed nations have therefore exhibited substantial variance for identical products (Frank 2001, Danzon and Towse 2003). We would expect national demand to be strongly influenced by per capita income. In wealthy nations, health care spending is a "wealth good," i.e., a mix of products and services for which consumers tend to allocate larger portions of income as wealth increases. Thus relative wealth accounts for a substantial portion of the disparities in health spending among advanced economies (Reinhardt, Hussey, and Anderson 2002). Several analysts have argued that in the absence of artificial constraints such as government price controls, patented drugs would tend toward prices that are roughly proportional to per capita GDP (Danzon and Towse 2003; ITA 2004, p. 16). Another factor may also be important, however. Some innovative new drugs are priced partly according to the savings they offer to health care systems. For example, a recently approved biotechnology drug for treating myelodysplastic syndrome, a rare blood disease, was priced at approximately $54,000 annually in the U.S. to reflect the costs of blood transfusions and other costly measures that the drug would prevent (*Wall Street Journal*, December 29, 2005). Other new drugs, notably the so-called targeted cancer drugs that attack certain forms of cancer cells (such as Herceptin, Gleevec, and Avastin) may tend to be priced to compete with existing treatments such as chemotherapy and its associated costs of monitoring and alleviating side-effects (cf. *New York Times*, May 11, 2001, on the initial price for Gleevec). Such costs are usually much lower abroad, often simply because prices of health care inputs are lower (Danzon and Furukawa 2003, Exhibit 6; Anderson, et al. 2003). Thus U.S. prices for drugs that reduce

health care costs may seem extraordinarily high in foreign nations where non-pharmaceutical costs are lower.[2]

Pricing far above marginal costs also offers the opportunity for individual nations to suppress prices through legal controls without endangering supply because manufacturers can continue to realize profits at prices that remain substantially above marginal cost even if they are lower than what would occur in an uncontrolled private market. Nations with price controls can in theory free-ride on non-price-controlled nations in the sense of providing a disproportionately low return to pharmaceutical R&D (Danzon 1998). There are reasons to suspect this actually happens. Total pharmaceutical manufacturer revenues through retail channels in Germany during 2004 were less than 13% of U.S. sales while Germany's GDP is about 22% that of the U.S.[3] The prospect of free-riding, with its adverse consequences for future drug development, was raised by then-FDA Commissioner Mark McClellan in a widely noted speech (McClellan 2003). A recent report by the International Trade Administration, part of the U.S. Department of Commerce, suggested that international price controls are substantially retarding the development of new drugs (ITA 2004).

Of special importance are new biotechnology drugs, including monoclonal antibodies that can treat previously untreatable forms of cancer while providing novel approaches to rheumatoid arthritis, M.S., and other illnesses. Such drugs (of which dozens are available but many more are in development) are both expensive to manufacture and tightly targeted at highly specific biological mechanisms. They are typically less susceptible to competition than traditional drugs because they are designed to address situations in which patients have few, if any alternatives (although this has been changing as the biotechnology sector continues to grow and thus foments competition in more lucrative markets). Biotechnology drugs could therefore prove more resistant than traditional small-molecule drugs to price controls.

In this article, we review earlier work on international pharmaceutical prices and then bring to bear a data set that permits us to explore questions not previously addressed. These

[2] We do not mean to suggest that reductions in other health care costs are, or should be, the primary factor in setting prices. For example, new drugs may offer benefits to employers (in foregone expenses for lost work time and other factors) and to patients (who may suffer less and live longer, quite aside from impact on health care costs).

[3] The *IMS Retail Drug Monitor* for 2004 reports total German revenues at $25.1 billion vs $174.5 billion in the U.S., but neither figure reflects rebates. As we note below, Germany imposed a 16% rebate for nearly all patented drugs purchased through public insurance (which accounts for 90% of the population) during 2004. As we explained earlier, unrecorded U.S. rebates were probably much less than the German rebates. If we reduce German revenues by 10%, they were a little less than 13% of U.S. revenues.

include the impact of therapeutic class competition and biotechnology status on price and revenue disparities for approximately 43 drugs in six nations: the U.S., Australia, Canada, France, Germany, and the U.K.

2. International Price Controls and Their Effects

Price control regimes

During the past two decades or so, all advanced economies except the United States have implemented comprehensive controls over pharmaceutical prices either directly or, in the case of the U.K., indirectly by means of profit ceilings (ITA 2004, appendix C; Danzon and Chao 2000). These price control regimes exhibit great variety (Kanavos 2002; ITA 2004, appendix C). A common element has been reference to price ceilings in other nations (sometimes called external reference pricing), as in Canada, where most drug prices cannot exceed the median price in seven designated nations. An increasingly common tool is reference to the lowest price within a therapeutic class (therapeutic class reference pricing) (Danzon and Ketcham 2004; ITA 2004, Appendix C). If a reference pricing class includes a drug with generic equivalents, so that all brands are reimbursed at the rate for the cheapest drug in the class, the effect is to reimburse patented drugs at levels far below prices in nations without this form of reference pricing. Several nations, including Australia, New Zealand, and the Canadian province of Ontario, have used this type of reference pricing (Australian Productivity Commission 2001, p. 26). Germany recently resumed this approach starting with the statin class of cholesterol-reducing drugs (Bandow 2005; VFA 2005; U.S.T.R. 2005, p. 11).

In some nations, such as France, patients using the higher priced drug must pay the entire price and sacrifice government reimbursement altogether. More typically, as in Germany, patients can ask for a higher priced drug and pay only the difference (Bandow 2005, VFA 2005). In any case, bans on direct-to-consumer advertising keep manufacturers from communicating directly to patients. Physicians would therefore have to take the time to explain to their patients why higher-priced drugs are worth the difference. There appears to be little evidence that physicians do this, nor is there any reason why physicians would be compensated for their time in doing so (cf. Danzon and Chao 2000, p. 320). This is despite the fact that several large clinical trials have demonstrated substantial morbidity and mortality differences even in such

crowded therapeutic classes as the statin drugs (Topol 2004). The practical effect, therefore, is either that reimbursement rates serve as price ceilings or higher priced drugs suffer extreme losses in market shares and revenues. This is borne out by experience in Germany, where therapeutic class reference pricing has been applied to the statin class of cholesterol-reducing drugs since Jan. 1, 2005, with drastic effects on brand sales (*Wall Street Journal*, May 2, 2005). German physicians who wish to inform patients of the clinical benefits of more powerful statins would have to deal with a government report that essentially dismisses the leading evidence on that point (Wess 2005).

The variety in price control regimes reflects the fact that no single conceptual foundation for price controls has yet to be advanced and carefully explored (Calfee 2001). For example, although Australia and other nations have recently cited cost-effectiveness as a standard for price ceilings (ITA 2004, appendix C; Henry, Hill, and Harris 2005), neither the theoretical nor the practical relationship between cost-effectiveness and price ceilings has been specified (Calfee 2001). What is known is that cost-effectiveness analysis provides a clear path toward price negotiations and permits the introduction of other factors such as total costs and the "rule of rescue" (i.e., paying more attention to the needs of patients who are widely identified as individuals) (Henry, Hill, and Harris 2005).

National price control mechanisms also change frequently. The ITA report, for example, documents substantial changes in price regulations in some nations within just a few years (ITA, Appendix C). Germany is a good example of the fluidity of price controls. As we describe below, in 2003, Germany required a 6% rebate for almost all patented drugs purchased through public insurance plans (which cover approximately 90% of the population). The rebate was increased to 16% in 2004 and then reduced back to 6% in January 2005 when a broader therapeutic class reference pricing plan was implemented.

International price comparisons

In a landmark analysis of prices in the year 1992 (actually, for October 1991 through September 1992), Danzon and Chao (2000) found that pharmaceutical prices in large developed nations were not consistently lower than those in the U.S., although they did not separate patented drug prices from generic drug prices. An update published in 2003 used 1999 prices. It found Laspeyres price indices for on-patent drugs in Canada, France, Germany, and the U.K.

(after assuming an 8% discount from invoice prices in the U.S.) were 0.64, 0.61, 0.73, and 0.74, respectively, i.e., from 26% to 39% lower than in the U.S., although Japan's prices were generally higher (Danzon and Furukawa 2003, exhibit 4).[4] The discounts from American prices tended to be substantially more than proportional disparities in per capita GDP. Using different methods and a much smaller data set, Anderson, et al. (2004) found similar disparities in international prices (also see the comment by Danzon 2004a).

In 2004, the International Trade Administration (ITA, part of the U.S. Department of Commerce) and the U.S. Department of Health and Human Services (USDHHS 2004) published separate analyses of 2003 prices in 9 OECD countries, applying similar methods to those of Danzon and her co-authors. (As in the Danzon, et al. studies, foreign prices were calculated from revenue and volume data provided by the market research firm IMSHealth.) The ITA (p. 38) reported that pharmaceutical prices in seven advanced nations were between 35 and 48 percent lower than U.S. prices.[5] Again, these relative prices were substantially below relative per capita GDP levels (see Table 3).[6] Although they began with the same IMS data set, the HHS analysts arrived at somewhat different results because they used different criteria in determining which drugs to keep in their final data set. The ITA analysis dropped all drugs facing generic competition in the U.S. while the HHS study retained those drugs but used the prices of the original branded drugs while ignoring generic prices. Because manufacturers typically avoid reducing branded prices when generics enter the market (Reiffen and Ward 2005), the differences between the ITA and HHS results were small (see Table 3).

Thus on the whole, research reveals large international price disparities, with average prices in large developed nations (except Japan) about 30 to 50 percent lower than American prices. Moreover, these disparities have grown over the past fifteen years and have come to substantially exceed disparities in per capita GDP.

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[4] Price indices necessarily assign weights to the prices of each individual drug in the group of drugs for which an index is sought. Laspeyres price indices weight the various drugs in proportion to U.S. revenues. Paasche price indices, on the other hand, weight the various drugs in proportion to revenues in the relevant foreign nations. Obviously, the two indices will usually be different. When foreign nations use a very different mix of drugs, the two indices can diverge to a substantial degree, as we found in some of the results discussed below.

[5] Unless otherwise noted, we generally refer to Laspeyres price indices, which are constructed by weighting each drug by U.S. quantities in terms of S.U.'s, or Standard Units, as defined by IMS Health.

[6] The ITA report used per capita GDP measures from the IMF that did not take into account purchasing power parity, the most widely accepted measure of comparative GDPs. The ITA report then compared the IMF per capita GDP measures with Fisher price indices rather than Laspeyres indices, as we do. The Fisher indices are the geometric mean of Laspeyres and Paasche indices and thus are higher than Paasche indices and lower than Laspeyres indices. Our Table 3 shows relative per capita GDP based on purchasing power parity.

The Effects of price controls

A small literature has addressed the impacts of international price controls on pharmaceutical industry cash flow, profits, and drug development (Vernon 2005; Giaccotto, Santerre, and Vernon, 2003; Santerre and Vernon 2005). The 2004 ITA report estimates that by suppressing prices below natural levels (which are assumed to be proportional to per capita GDP), price controls in several advanced economies reduce profits and cash flow sufficiently to reduce the introduction of new chemical entities by approximately 2.7 to 4.1 entities per year (ITA 2004, p. 31).

Danzon, Wang, and Wang (2005) address a different question, the extent to which price controls delay the introduction of new drugs into nations with more stringent controls. They find that the combination of external reference pricing and the threat of parallel trade from low-price to high-price nations causes pharmaceutical firms to delay or forego the launch of new drugs, particularly in countries where controls greatly reduce drug prices.

Are price disparities different for different drug classes?

The empirical studies just summarized all report only the differences between average prices in the U.S. and average prices in each of several foreign nations. None of the studies examine how price disparities vary across individual drugs or therapeutic classes (including classes with recent generic entry), or how price disparities vary between traditional small-molecule drugs and large-molecule biologicals (most of which involve biotechnology). Similarly, analyses of the impact of price controls usually assume that price differentials engendered by price ceilings are uniform throughout the patented pharmaceutical market. Because the pharmaceutical market is changing rapidly under the impact of generic entry and biotechnology, a natural question is whether international price disparities (and their effects) are substantially different for different parts of the pharmaceutical market.

3. International Price Disparities: Basic Results

We began with the list of the top-selling 55 drugs in the US for 2004 (NDCHealth 2005). Four drugs were excluded at the outset: two narcotic analgesics (because they are controlled

substances and thus subject to atypical market forces) and rofecoxib (Vioxx) and valdecoxib (Bextra), which are no longer on the market. We also excluded drugs for which there was substantial generic competition in the United States throughout 2004 because our interest is in how foreign prices compare with drugs still under patent in the U.S. Seven drugs were excluded on these grounds.[7] After taking account of the fact that one drug was marketed under two different brands (Procrit and Epogen, for which we combined the data), we were left with the 43 molecules listed in Appendix 1.

We obtained prices and quantities for the 43 drugs in each nation from an IMSHealth MIDAS data set. For each drug, IMS provided a weighted average price per standard unit (which is normally the smallest common dosage), including prices from authorized licensees where relevant.[8] A widely noted problem with IMS price data for the American market is that they do not reflect rebates, which are normally not recorded in the invoices from which IMS derives its price estimates (see Danzon and Furukawa 2003). The authors of the HHS report, however, had access to Medicaid "best price" data (which are required by law to reflect rebates). The authors concluded that at least for non-Medicaid prices, IMS data are quite accurate.[9] Following HHS, and in contrast to earlier work, we also assumed that IMS prices for non-Medicaid purchasers need not be discounted to provide more accurate data.[10]

[7] We did retain a few drugs for which IMS data included very small sales from sources other than the pioneer firm or its licensees. These drugs obviously did not face significant generic competition.

[8] Our IMS data set consisted of a single weighted price (along with revenues) for each drug in each nation. Prices were per IMS-defined standard unit (S.U.), a widely used measure. Prices across dosages, pack size, and so on, were weighted by volume by IMS. The ITA and HHS studies, as well as the Danzon studies, used far more extensive (and far more expensive) IMS data sets with separate prices and revenues for each pack size, etc. Thus we relied upon IMS's own weighted averages for each drug in each nation rather than calculating our own. Danzon's articles in the references section provide some discussion of the potential impact of using less aggregated measures, which permit direct comparisons for, e.g., specific dosages.

[9] See the discussion at HHS 2004, p. 70. HHS used non-public data to adjust prices paid by Medicaid to reflect non-public rebates. This discussion noted that for the top-selling drugs in their data set, their analysis indicated that "market prices including Medicaid are slightly less than the IMS invoice prices for comparable transactions." The report noted at p. 115 that for non-Medicaid prices of branded products, "the CMS totals were about one percent higher than the IMS totals . . ." The complicated laws on Medicaid drug prices are described in CBO 2005.

[10] Danzon and Furukawa 2003 (p. 526) used a complicated method to adjust IMS prices for the U.S. to reflect unrecorded manufacturer discounts. Their method resulted in an average discount of eight percent from IMS prices, which they note was comparable to contemporary estimates of unrecorded rebates. We also note that the ITA analysis excluded prices paid to Medicaid. We could not do that because the data set we used simply provided all ex-manufacturer prices paid by wholesalers, including ones who in turn sold to Medicaid. Had our data also included rebates paid by manufacturers to Medicaid, they would in effect have included some prices that were substantially below private market prices. But our data excluded rebates paid only to Medicaid. The net effect is that our price data are probably very comparable to the ones ITA relied upon in their analysis.

IMS data also do not reflect rebates in foreign nations. That has generally not been a problem because foreign rebates have been rare. Germany has become an exception, however. In 2004, Germany imposed a 16% rebate for nearly all patented drugs purchased through public insurance.[11] This was an increase from 6% in 2003. In January 2005, the rebate was dropped back to 6%, partly because of a substantial expansion of therapeutic reference pricing. These rebates are not captured in the IMS data, but in 2004, at least, the rebate was large enough to materially affect international comparisons. In 2001, approximately 90% of German consumers received pharmaceuticals through public insurance.[12] We assume that the same proportion of patented drug revenues was subject to the rebate. We therefore reduced all prices and revenues in Germany by 14.4% (90% of 16%).

In calculating price indices, we excluded prices from nations in which a generic was available for specific drugs because, again, we are interested in the effects of price controls on prices for patented drugs.[13]

With these restrictions and adjustments, we calculated both Laspeyres and Paasche indices of relative prices, where the Laspeyres indices were weighted by U.S. volumes, and Paasche, by foreign volumes. The results are presented in Table 1. Laspeyres indices in Australia and Germany (the latter with the 16% rebate in effect) were about 0.52 while those in the other three nations clustered around 0.60, i.e., somewhat more than half the U.S. level. Paasche indices were substantially lower, reflecting the tendency of foreign nations to consume relatively larger quantities of lower-priced brands.[14]

[11] U.S.T.R. 2005, p. 11. The exception was drugs already subject to reference pricing. We learned from industry sources that all of the drugs we examined were in fact subject to the rebate, with the exception of sildenafil (Viagra), which was not eligible for reimbursement under the Statutory Health Insurance system.

[12] See Busse 2004, n. 1, who reports 88% for public insurance and 2% for "free governmental health care (for example, police officers . . .)".

[13] So, for example, in calculating price indices, we excluded Zocor prices in Germany, where a generic was available, but included Zocor prices in Australia, where no generic was available.

[14] The data set included a very low and apparently anomalous bulk price for rituximab in the U.K.; we deleted that component from the U.K. rituximab price.

Table 1
Relative Pharmaceutical Price Indices
for 43 Drugs in Five Developed Nations (U.S. = 1.00)

	U.S.	Australia	Canada	France	Germany	U.K.
Laspeyres	1.00	0.52	0.61	0.58	0.53	0.59
Paasche	1.00	0.41	0.50	0.43	0.46	0.50

See Appendix for a list of the 43 drugs.

We noted that spontaneous differential pricing could tend to track with relative per capita GDP levels. Table 2 presents relative price indices, relative per capita GDP, and the ratios of the first to the second. Relative prices in all five nations are well below relative GDP levels, with Australia at 0.66 of relative per capita GDP and the others concentrated between 0.74 and 0.77. We noted earlier, however, that because foreign health care services tend to be priced much lower than U.S. levels (even more so than drug prices are, according to Danzon and Furukawa 2003), manufacturers unconstrained by controls could tend to price below relative per capita GDP for drugs that yield cost savings elsewhere in health care systems (because these cost offsets would be worth less in foreign nations). This could account for part of the disparity between relative per capita GDP and relative drug prices, but we see little reason to think it accounts for the bulk of it. At any rate, we will see later that price disparities depend strongly on what kind of drugs are being compared.

Table 2
Relative per capita GDP and Pharmaceutical
Price Indices for 43 Drugs in Five Developed Nations

	U.S.	Australia	Canada	France	Germany	U.K.
per capita GDP ratio to U.S. (2004)	1.00	0.79	0.79	0.75	0.72	0.79
Laspeyres	1.00	0.52	0.61	0.58	0.53	0.59
ratio of Laspeyres to relative per capita GDP	1.00	0.66	0.77	0.77	0.74	0.75
Paasche	1.00	0.41	0.50	0.43	0.46	0.50
ratio of Paasche to relative per capita GDP	1.00	0.52	0.63	0.57	0.64	0.63

See Appendix for a list of the 43 drugs. Per capita GDP data using PPP comparisons are from the OECD, National Accounts of OECD Countries, Main Aggregates, Vol. 1, reported at current prices in U.S. dollars based on current purchasing power.

Table 3 presents our results along with earlier results from Danzon and Furukawa (2003) and ITA (2004). Except for Australia, where our results are 13 percentage points lower, our findings are within three to six percentage points of the ITA results for Laspeyres indices, with Canada, France, and the U.K. slightly higher (and Germany would have been substantially higher without the 16% rebate). These differences reflect a different mix of drugs (including two new biotech drugs), different weights (because of changes in revenues), the use of more aggregated IMS data, and the 16% rebate in Germany.[15] Note that the large disparity between the ITA's estimated Laspeyres and Paasche indices (0.65 vs 0.38) for Australia indicates that Australian usage is unusually sensitive to prices.

[15] The German rebate was 6% in 2003. The ITA report does not mention the rebate; we have been informed by former ITA staff that the rebate was not taken into account in the ITA's calculations. We noted earlier that our IMS data set was aggregated to the molecule level for each nation, whereas the ITA and HHS staff acquired far more detailed data for each pack size and dosage, from which the staffs calculated weighted price indices. We also used data for 2004 instead of 2003, resulting in a different mix of drugs and different weights for the same drugs. Four drugs on the ITA list are not on ours (fluticason, interferon beta 1A, ribaviron, and rofecoxib), and six were on our list but not ITA's (aripiprazole, cetirizine, darbepoetin alfa, escitalopram oxalate, lamotrigine, and pegfilgrastim).

Table 3
Recent Estimates of Relative Pharmaceutical Price Indices
for 43 Drugs in Five Developed Nations (U.S. = 1.00)

	Australia	Canada	France	Germany	U.K.
Our results					
relative per capita GDP (2004)	0.79	0.79	0.75	0.72	0.79
Laspeyres (2004)	0.52	0.61	0.58	0.53	0.59
ratio of Laspeyres to relative p.c. GDP	0.66	0.77	0.77	0.74	0.75
Paasche (2004)	0.41	0.50	0.43	0.46	0.50
ITA (2004)					
relative per capita GDP (2003)	0.80	0.81	0.74	0.72	0.79
Laspeyres (2003)	0.65	0.57	0.55	0.55	0.53
ratio of Laspeyres to relative p.c. GDP	0.81	0.70	0.74	0.76	0.67
Paasche (2003)	0.38	0.51	0.43	0.49	0.43
HHS (2004)					
Laspeyres (2003)	0.67	0.57	0.53	0.57	0.56
ratio of Laspeyres to relative p.c. GDP	0.84	0.70	0.72	0.79	0.71
Danzon and Furukawa (2003)					
relative per capita GDP (1999)	0.77	0.81	0.73	0.73	0.73
Laspeyres (1999)		0.64	0.61	0.73	0.74
ratio of Laspeyres to relative p.c. GDP		0.79	0.84	1.00	1.01

See Appendix for a list of the 43 drugs. Parentheses indicate the year of the data. Our results are for year 2004 prices; ITA (2004) and HHS (2004) are for 2003 prices; Danzon and Furukawa (2003) is for 1999 prices. Per capita GDP data using PPP comparisons are from *OECD Factbook* 2005, reported at current prices in U.S. dollars based on current purchasing power.

Danzon and Furukawa (2003)'s analysis of 1999 data yielded consistently higher relative prices than in our study and in the ITA report. Those 1999 relative prices were in turn substantially higher than those found by Danzon and Chao (2000) for 1992 prices, which are not shown in the table (that estimate included generics, however). Comparing results for 2003 and 2004 data with that for 1999 and 1992 data, international pharmaceutical prices have been declining relative to U.S. prices and, roughly speaking, have dropped from approximate parity with relative per capita GDP in 1999 to levels substantially below relative per capita GDP in 2003 and 2004.

4. What Influences Price Differentials?

We explored several factors that could affect the extent to which U.S. and foreign prices diverge. We report here the results of a preliminary analysis including simple cross-tabulations and regressions; a subsequent version will include additional econometric results. One obvious question was whether some nations were more stringent than others in their controls over prices. We found mixed evidence. Three nations were clustered within a band of three percentage points around a relative price index of 0.60, while Australia and Germany were at approximately 0.52 (using Laspeyres indices). When we excluded biotech drugs (as reported below) the range was slightly larger, with Australia and France having the lowest non-biotech prices (0.45), followed by Germany (0.48), Canada (0.50), and the U.K. (0.54). In the regression exercise reported below, which takes account of the relative uniqueness of drugs and whether a drug is classified as biotech, we estimated a model that included dummy variables for each foreign nation. Although the estimated coefficient for Australia was negative (representing a decline of four percentage points), its statistical significance was very marginal ($p = 0.30$). Coefficients for other nations were not close to being significantly different from zero. In one respect, however, national differences were striking. When we separated drugs according to relative uniqueness, as described next, relative prices in Canada and France were well above those in Australia, the U.K., and especially Germany. For biotechnology drugs, the national configuration was similar but with even more striking differences in relative prices.

Relative uniqueness

Another possibility is the influence of therapeutic class competition, i.e., competition from drugs employing a biologically similar mechanism within a therapeutic category. The presence of multiple brands within a single class should bolster competitive forces driving prices down in the U.S. market while providing foreign price controllers with leverage in setting or negotiating price ceilings. To explore this topic, we classified drugs into three classes of relative uniqueness. For many drugs, this was a relatively straight-forward process, as for example in categorizing proton pump inhibitors into the least-unique category. Other drugs, of course, involved judgment. We classified the three statins in the least unique category, while putting the SSRI and SNRI antidepressants in the middle category along with atypical antipsychotics, two antibiotics, and several other therapeutic categories including two TNF-inhibitors used to treat rheumatoid arthritis (cf. *Boston Globe*, Oct. 14, 2004, on competition in this category). All biotech drugs fell into the most-unique category.

Appendix 1 lists these classes and the drugs that belong to them. We then calculated separate price indices for each degree of uniqueness. Table 4 presents the results.

Table 4
Relative Price Indices for 43 Drugs
According to Relative Uniqueness*

	Australia	Canada	France	Germany	U.K.
Least unique					
Laspeyres	0.40	0.52	0.40	0.41	0.45
Paasche	0.41	0.53	0.38	0.41	0.42
Moderately unique					
Laspeyres	0.44	0.44	0.46	0.51	0.59
Paasche	0.39	0.41	0.38	0.46	0.56
Most unique					
Laspeyres	0.75	0.88	0.96	0.65	0.74
Paasche	0.45	0.62	0.81	0.57	0.60
relative per capita GDP (2004)	0.79	0.79	0.75	0.72	0.79

* See Appendix for a list of the 43 drugs classified by relative uniqueness.

Relative prices increase as we move from least unique to most unique, especially between moderately and most unique, with the sole exception that least-unique prices were somewhat higher than moderately unique prices in Canada. Also, the disparities between Laspeyres and Paasche indices increase as we go from the least-unique to the most-unique categories. This is presumably because nations adjust prescribing patterns among drugs in response to relative prices across drug categories. Also notable is that Laspeyres indices are roughly comparable with relative per capita GDP except for France, where prices were well above that benchmark. A natural question is why prices of less-unique drugs tend to be lower abroad than in the U.S. We address that question in the discussion section.

Biotechnology vs. traditional drugs

Biotechnology drug pricing in international markets may work differently from pricing for traditional drugs (often referred to as "small molecule" drugs although some biotech drugs are small molecules rather than proteins, or large molecules). For one thing, manufacturing costs are typically much higher for biotechnology drugs. Perhaps more important, however, is the fact that many of these drugs ─ most monoclonal antibodies for cancer, for example ─ attack conditions that are otherwise nearly impervious to treatment. These drugs usually have no close substitutes. Anecdotal evidence suggests that some biotech drug manufacturers maintain a single world price in developed nations regardless of national price controls (cf. Columbia Business School 2002; *New Zealand Herald*, July 30, 2002). To explore biotechnology drug pricing in the U.S. and foreign markets, we sought to classify the drugs we studied as being biotech or non-biotech. Unfortunately, there is no well-accepted definition of a biotechnology drug. Although most biotech drugs are complex proteins ─ "large molecules" instead of "small molecules" ─ not all are. The cancer drug Gleevec is an example of a small-molecule drug (administered in pill form) that is indisputably the result of sophisticated biotechnology research methods (*New York Times*, May 8, 2001; Novartis 2001; Stephenson 2001). We therefore relied upon the Biotechnology Industry Organization's registry of approved biotechnology drugs. Seven of our drugs were classified as biotech; these are indicated with an asterisk in Appendix 1.

Table 5 presents relative price indices for biotech and non-biotech drugs. The differences are striking. The gulf between biotech and non-biotech Laspeyres indices is very large. Biotech drug prices in Canada and France are actually above U.S. levels, and only Germany (at 0.71) is below 80% of U.S. levels. On the whole, the biotech drugs in our sample were priced within ten percent or so of U.S. prices and (except Germany, again) were on average priced above relative per capita GDP. On the other hand, non-biotech prices were roughly at 50% of U.S. levels. In other words, relative to U.S. prices, foreign biotech price indices were nearly twice small-molecule drug price indices. But that is when we look at Laspeyres indices. The story for Paasche indices is different. While Paasche non-biotech indices are slightly lower than Laspeyres indices, as one would expect, Paasche biotech indices are substantially lower than Laspeyres indices, averaging about two-thirds to 70% of U.S. levels (with Australia at 52%). This reflects the tendency in some nations to avoid rapid use of newer, more expensive biotech drugs, a topic that we take up later.

Table 5
Laspeyres Relative Price Indices for 43 Biotech and Non-Biotech Drugs in Five Developed Nations

	Australia	Canada	France	Germany	U.K.
Biotech					
Laspeyres	0.83	1.04	1.18	0.71	0.80
Paasche	0.52	0.67	0.89	0.56	0.68
Non-biotech					
Laspeyres	0.45	0.50	0.45	0.48	0.54
Paasche	0.40	0.48	0.39	0.45	0.48

See Appendix for a list of the 43 drugs.

Regression analysis

We also employed regression analysis to assess the relative power of the factors just outlined. We did not model the negotiating processes underlying drug prices in either the U.S. or in nations with price controls. We assumed that those processes would support a simple model in which for each individual drug, the ratio of each foreign price to the U.S. price could be treated as a function of several independent variables.[16]

We constructed a scalar variable called "uniqueness" that took the value of 0, 1, or 2 according to how each drug was classified. We also included a biotechnology dummy variable that took the value of one for biotechnology drugs and zero otherwise.[17]

Thus our model was:

[16] We used the STATA econometric program to employ OLS (ordinary least squares) with robust standard errors. Because the dependent variable (the ratio of foreign prices to U.S. prices) is truncated in the sense of not permitting negative values, we tested the validity of OLS by using the regression results to predict the values of price ratios. No predicted values were negative, indicating that OLS is a satisfactory method.

[17] Recall that we tried entering dummy variables for each nation, but dropped them because none of the coefficients were statistically significant and the other results were essentially unchanged.

$$\mathbf{R} = K + \beta_u \text{Uniqueness} + \beta_b \text{Biotechnology} + \varepsilon$$

where

R = ratio of foreign to U.S. manufacturer prices for each drug in each foreign nation

K = constant

Uniqueness

0 = least unique: very similar to other molecules
1 = moderately unique
2 = most unique

Biotechnology = biotechnology drug dummy = 1 for biotechnology drug

The results are presented in Table 6:

Table 6
Determinants of Relative Drug Prices
for 43 Drugs in Five Nations Compared to U.S. Prices

Variable	Coef.	Std. Error	p-value
Constant	0.395	0.020	0.00
Uniqueness	0.127	0.028	0.00
Biotech	0.203	0.079	0.01

n = 189, r^2 = 0.301, F(2,186) = 27.18 (p = 0.00). The nations are Australia, Canada, France, Germany, and the U.K.; see Appendix for a list of the 43 drugs.

Recall that the dependent variable is the ratio of manufacturer prices for each drug in each relevant foreign nation to U.S. prices. The basic statistical measures (r^2 and the goodness-of-fit F statistic) indicate a respectable degree of explanatory power.[18] All estimated coefficients (including the constant) are highly significant, as is the F statistic (assuming that a coefficient is statistically significant if its p-value is 0.05 or less).

The results are very suggestive and they largely reinforce the results in the simple tables provided above. The constant term of 0.40 represents relative prices of drugs that are least

[18] Because the dependent variable is truncated at a lower bound of zero, we exercised a STATA routine to check for negative predicted values (which could cause biased parameter estimates). No negative predicted values were found. We therefore felt comfortable in using OLS with standardized beta coefficients and robust standard errors.

unique (and none of which are biotech drugs). Drugs that are more unique have significantly and substantially higher prices, so that after controlling for biotech status, drugs in the most unique category are about 25 percentage points higher than those in the least unique category.[19] Biotechnology status adds another 20 percentage points, suggesting foreign biotech prices are at roughly 86% of U.S. prices. Thus relative biotech drug prices were well above relative per capita GDP. This intriguing observation is taken up in the next section.

5. Revenues of Biotech and Non-Biotech Drugs

Governments in wealthy nations other than the United States are not only would-be price controllers in pharmaceutical markets, but they are also the exclusive or dominant payers. Thus governments can control usage even when they cannot control prices. The fact that foreign biotechnology drug prices were roughly at parity with U.S. prices (and well above relative per capita GDP ratios) raises the question of how foreign biotech drug usage compares with U.S. patterns. Table 7 presents total revenues by nation for biotechnology and non-biotechnology drugs in our sample, along with biotechnology shares of national revenues.

These results are of considerable interest. Recall that relative to the U.S., foreign biotech drug prices are much higher than non-biotech prices. That means that if drug usage patterns in the five foreign nations closely tracked those in the U.S., biotech drugs should account for a much larger share of foreign revenues than of U.S. revenues. But we observe the opposite: biotech drugs capture only 14% of foreign revenues compared to 17% of U.S. revenues.

[19] The most-unique category was coded with a uniqueness variable equal to 2, as opposed to 0 for the least-unique category. Hence to calculate the relative prices of the most-unique drugs we add twice the 0.127 coefficient of the uniqueness variable, yielding approximately 0.40 plus 2 X 0.13, or 0.66.

Table 7
Foreign vs U.S. Revenues for
43 Biotechnology and Non-Biotechnology Drugs
(millions of $US)

	Total revenues	Biotech revenues	Biotech share	Non-Biotech revenues	Non-Biotech share
Australia	1,785	198	0.11	1,587	0.89
Canada	3,128	409	0.13	2,719	0.87
France	5,116	856	0.17	4,260	0.83
Germany	3,178	508	0.16	2,670	0.84
U.K.	4,040	360	0.09	3,680	0.91
Foreign total	17,247	2,331	0.14	14,916	0.86
U.S.	91,904	15,530	0.17	76,374	0.83
Total	109,151	17,861	0.16	91,290	0.84
Foreign Share of revenues	0.16	0.13		0.16	

See Appendix for a list of the 43 drugs. Some totals may not add up due to rounding error.

6. Discussion

In our analysis of 43 top-selling drugs in year 2004 in the U.S., Australia, Canada, France, Germany, and the U.K., relative price indices were similar to those estimated in the ITA and HHS studies of top-selling drugs in 2003 even though we used a different mix of drugs and a more aggregated data set, and took account of a substantial new rebate in Germany. We found, as did ITA and HHS, that relative prices in these five foreign nations tended to be about 52% to 62% of U.S. prices. These ratios were well below relative per capita GDP (75% to 79% of U.S. levels), an oft-mentioned benchmark for international drug prices. In contrast, earlier studies

using international price data from 1999 and 1992 found relative prices roughly at parity or higher compared to the per capita GDP benchmark.

We found only modest differences across non-U.S. nations, with price indices ranging from 0.52 for Australia and 0.53 for Germany to 0.61 for Canada. One striking factor, however, was the 16% rebate that Germany imposed during 2004. It dropped Germany from having the highest prices (along with Canada) to nearly the lowest among the five nations. The 16% rebate applied only during 2004 before reverting to 6%, but a more aggressive form of therapeutic reference pricing was introduced for 2005. The prospect of future rebates will surely stiffen the negotiating stances of manufacturers of drugs in more-unique (and thus less competitive) classes, even as prices in more competitive classes are pushed further down toward the prices of newer generics in the same class.

Toward bifurcated international pricing: monopsonies and bilateral monopolies

Most of our analysis focused on how price disparities varied across broad categories of drugs. Some findings are striking. Dividing our sample into three groups of least-unique, moderately-unique, and most-unique drugs, relative prices were slightly lower for least-unique drugs than for moderately-unique ones (except in Canada), but relative prices for moderately-unique drugs were far lower than for the most-unique category of drugs. Comparing non-biotech and biotech drugs, price indices for non-biotech drugs were only about 0.50 whereas indices for the seven biotech drugs in our sample ranged between 0.69 (in Germany after its 16% rebate) and 1.18 (in France). We also found large disparities between Laspeyres and Paasche indices for the most-unique drugs and also for biotech drugs, suggesting substantial adjustments in the mix of prescribed drugs in foreign nations faced with large relative price differences across drugs.

Examining revenues rather than prices, biotech drugs accounted for only 14% of foreign revenues versus 16% of U.S. revenues even though foreign biotech drug prices are relatively much higher than non-biotech prices. The biotech component of revenues was especially low in Australia, Canada, and the U.K. In France and Germany, biotech drugs accounted for essentially the same proportion of revenues as in the U.S., but that, too, represents disproportionately slower uptake of biotech drugs because relative prices in those nations were substantially higher for biotech than for non-biotech drugs. Foreign shares of total biotech revenues were correspondingly low. In fact, the foreign share was a remarkably low 7% for Procrit and 8% for

Neulasta (not shown in the table). These nations simply did not avail themselves of the biotech drugs in our sample to anywhere near the extent that the U.S. did.

Why did prices of less-unique drugs tend to be so much lower abroad than in the U.S.? We offer some thoughts about the possible impact of several factors. One is that some of these drugs faced more competition abroad from generic versions of older drugs in the same therapeutic class. Statins are an example: both Zocor (simvastatin) and Pravachol (pravastatin) were available in generic form for at least part of the year in Canada, Germany, and the U.K. but not in Australia, France, and the U.S. Although we avoided direct comparisons between prices of on-patent drugs in the U.S. and generic versions of the same drug abroad, the presence of a generic can strongly affect pricing of other patented drugs in the same class. But we doubt that generic competition alone can explain the low prices for least-unique and moderately-unique drugs. For one thing, many of these drugs faced no more generic competition abroad than in the U.S. Moreover, the U.S. generic market generally features more competition and lower prices than in most if not all of the five foreign nations (Danzon and Ketcham 2004**)**. Nonetheless, the differential impact of off-patent drugs in foreign versus U.S. markets appears to be a little explored topic (which we could not address because of limitations in our data set).

The size of the buyers was certainly irrelevant. Each of the three largest American pharmacy benefits managers (PBMs) negotiate prices for larger volumes of prescription drugs than the entire Australian or Canadian health care systems. A crucial factor, however, is the U.S. competitive environment, which is very different from that elsewhere. Even the largest American PBMs must compete among themselves. A PBM that is unable to reach agreement on prices for a popular member of a therapeutic class must take account of the fact that its clients (managed care organizations and individual employers, for example) can easily turn to another PBM. No such competition exists in the other nations. This suggests that a single payer arrangement rather than volume is the driving force in price negotiations over drugs facing therapeutic competition. The fact that the small nation of New Zealand is known for its low drug prices reinforces this observation.

Thus the main factor in lower prices for competitive, non-unique drugs appears to be monopsony power (as has been argued by, among others, ITA 2004 and Danzon 2004b). Central governments essentially act as monopsonistic purchasers even when they only set prices for purchases by private organizations or provincial governments. This fact clearly shapes the

impact of generic competition within classes. For example, we noted that Germany sometimes links branded drug prices to generic prices in the same therapeutic class. On the other hand, monopsonies are rare in American pharmaceutical markets, restricted to a few federal agencies such as the Veterans Administration. We note, however, that monopsony power does not operate alone in foreign nations. The fact that manufacturers cannot communicate directly to patients (and are often greatly restricted when communicating to physicians) is also important. The inability to convey significant differences among competing brands has the effect of making drugs within a class seem more similar than they really are, thus reinforcing monopsony power.

In contrast, highly unique drugs, a category that includes most biotech drugs (so far, at least), are marketed in situations that approximate a bilateral monopoly, i.e., a single buyer and a single seller. This appears to explain why foreign prices of highly unique drugs are so much higher than those of less-unique drugs relative to U.S. prices. For the most-unique drugs, monopsony power is arrayed against monopoly power, leaving little if any role for price controls in the usual sense.

What happens when two biotechnology drugs actually compete rather closely? Our data show that the two TNF-inhibitors (for rheumatoid arthritis) tend to have higher prices abroad than in the U.S. Whether price competition in the U.S. will be sharper than in foreign nations as other biotechnology drugs begin to face competition (as most of them surely will; see Flanagan 2006) remains to be seen.

Lower prices, higher profits?

In some nations, biotech drug prices were probably well above the levels that would maximize profits. We noted earlier that on average, profit-maximizing prices for biotech and other highly unique drugs would probably be a little less than proportional to per capita GDP because the health care resources these drugs sometimes replace tend to cost less than in the U.S. (making the drugs relatively less valuable). But in our sample, biotech prices were closely aligned with relative per capita GDP in Australia, Germany, and the U.K., and remarkably, were far above that benchmark in Canada and France, where prices on average exceeded those in the U.S. At the same time, biotech drugs generated less than proportional revenues compared to non-biotech drugs. These circumstances strongly suggest that if the manufacturers charged

lower prices for biotech drugs abroad, they would increase both revenues and profits.[20] (Essentially the same reasoning explains why firms normally tend to price most pharmaceuticals lower in nations with lower per capita incomes; again, see Danzon and Towse 2003).

Some firms seem to pursue a policy of charging a single price in all advanced nations (and have said as much; see Columbia Business School 2002 on the cancer drug Gleevec.) A natural question is whether they pursue the profit-maximizing single price across nations. The fact that these five foreign nations accounted for only 13% of the revenues of the biotech drugs in our sample seems to suggest that prices are probably close to the profit-maximizing level for the U.S. At any rate, given how small foreign revenues are, we can be reasonably confident that biotech drugs were priced well above profit-maximizing levels in foreign nations, and presumably far above the prices that those nations would have imposed if they could exercise the same controls over biotech prices that they exercise for more traditional drugs.

One must ask why manufacturers would avoid charging lower prices abroad even though cutting prices would probably increase profits. We suggest that at least one force, and perhaps the primary one, is domestic politics. Most proposals to control drug prices in the U.S. are keyed to prices in Canada and other foreign nations, either indirectly through mass drug importation or directly by linking U.S. and foreign prices. Legislative proposals to permit unrestricted importation of drugs from price controlled nations have received strong public and political support. The District of Columbia recently passed a law (later overturned in the courts) to directly link domestic drug prices to foreign prices (D.C. 2005), and the state of West Virginia has considered similar legislation (West Virginia Cost Pharmaceutical Management Council 2004). The National Legislative Association on Prescription Drugs (2005) cites both measures in its list of model legislation for state legislatures.

Manufacturers presumably take into account the possibility that charging lower prices for expensive new drugs in wealthy foreign nations will create pressure for lower prices at home. Providing France with a 40% discount for a biotech drug costing $30,000 per treatment, for example, seems quite different from charging 40% less for a drug that costs only $70 a month.

[20] This conclusion depends on two other factors. One is the magnitude of marginal costs of manufacturing and distribution. We assume that marginal costs of biotech drugs are well below U.S. prices even though marginal costs are typically higher for large-molecule biotech drugs than for small-molecule drugs. We also assume that physicians in the foreign nations are not more reluctant than American physicians to prescribe biotech drugs. Current debates in Canada over lack of access to Herceptin, and in the U.K. over Herceptin, Femara and MabThera (two more

Firms may conclude that sacrificing a substantial proportion of foreign profits is a price worth paying to forestall price controls in the much larger U.S. market, especially when one considers that many biotech drugs are marketed by multi-product firms whose stake in pricing freedom extends far beyond a few biotech drugs. Overall, the effect is that foreign government price controls are not the only constraints on pricing. Domestic politics is also a factor.

Why don't the same political dynamics keep prices of less-unique drugs high? One reason is that international price disparities loom larger for biotech drugs simply because they tend to be more expensive than traditional drugs. Far more important, however, is competition. Manufacturers of less-unique drugs presumably cut prices at the insistence of foreign governments because they know that if they do not, one of their competitors will cut a deal and take away sales. Even if the manufacturer's only goal in price negotiations is to deter price controls at home, the same competitive forces that reduce profits abroad come into play.

Implications for pharmaceutical research and development

In exploring implications for pharmaceutical R&D, we begin with relatively less unique drugs. Almost all the brands in the least-unique and moderately-unique drug categories are follow-on drugs (sometimes called "me-too" drugs), i.e., drugs that exploit biological mechanisms very similar to those employed in pioneer brands. With total marginal costs typically on the order of 30% of U.S. prices (Danzon 1998, p. 296), the negotiation of foreign prices at 40%-50% of U.S. levels leaves a very modest payoff in foreign markets. The effect is to retard the development of follow-on drugs compared to what would occur without price controls.

This is unfortunate for two reasons. The most obvious is that most follow-on drugs provide substantial benefits to at least some patients in terms of improved side-effect profiles, superior efficacy, easier administration, and lower prices through competition (DiMasi and Paquette 2004; Lee 2004).

Probably more important, however, is the fact that research-based advances in drug therapy extend far beyond the discovery of pioneer members of entirely new classes of drugs. Essentially, this is because manufacturers of follow-on drugs can gain competitive advantage by

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biotechnology cancer drugs), suggest that physician reluctance is not a strong factor. Rather, the issue is cost and government funds; see Pearson and Rawlins 2005; *The Guardian*, Aug. 14, 2005; and *London Times*, Dec. 29, 2005.

performing research beyond what is necessary to gain marketing approval. The results may include new indications (such as stroke prevention by the statin class of cholesterol-reducing drugs) and broader efficacy (treating patients with lower baseline serum cholesterol levels, for example). Most of what we know about statins, cholesterol, and heart disease, for example, is a result of follow-on drug research undertaken for competitive reasons that continues today (Langreth 1998; Topol 2004; Nissen, et al. 2006). The selective serotonin reuptake inhibitors (SSRIs) are classified as antidepressants simply because depression happened to be the first of several diverse and unexpected applications revealed by follow-on drug research (Holden 2003).

The breadth of potential results from follow-on drug research reflects the fact that targeted biological mechanisms may play multiple roles in the human body. Rituximab (Rituxan), for example, was initially approved for non-Hodgkin's lymphoma, a form of cancer, but has been approved to treat rheumatoid arthritis. Etanercept (Enbrel), approved for rheumatoid arthritis, is used to treat psoriasis (Leonardi, et al., 2003). Infliximab (Remicade), first used to treat Crohn's disease, now treats arthritis and ulcerative colitis (Lipsky, et al., 2000; Rutgeerts, et al., 2005), while the HIV drug tenofovir (Viread) may be effective against Hepatitis B (Benhamou, Tubiana, and Thibault 2003). Another, more sweeping example is the entire NSAID (non-steroidal anti-inflammatory drug) class, which was developed to treat arthritis pain. Analysis of the biological underpinnings of these drugs suggest they may be useful for preventing cancer (Chau and Cunningham 2002) and perhaps other inflammation-related conditions such as Alzheimer's and diabetes. Research on these conditions is inherently expensive, requiring large, long-term clinical trials. That research has been funded almost entirely by the manufacturers of the Cox-2 inhibitors (Celebrex, Vioxx, etc.) because older NSAIDs are all off-patent (Calfee 2005).

The consequences of undermining incentives for follow-on drug development are comparable to forestalling research on entirely new types of drugs. An essential point is that research findings from follow-on drugs often support broader and more effective usage of older drugs, often drugs that are no longer being researched. Thus the lost benefits of forestalled class-level research can easily exceed the benefits of the therapeutic advances incorporated in the follow-on drugs themselves. The source of these adverse consequences from lower prices for follow-on drugs is the exercise of monopsony power, combined with an inability of

manufacturers to communicate with patients about the benefits of competing drugs (as discussed below).

We turn now to highly unique drugs including most biotech drugs. Here, prices abroad tend to be too high rather than too low, while foreign revenues and usage are unexpectedly and even drastically low. Manufacturers appear to sacrifice profits by maintaining rough parity with U.S. prices, presumably out of fear of the political consequences of charging lower prices in other wealthy nations. This is an indirect result of foreign price controls, caused by the threat that the U.S. will adopt foreign prices that are controlled at levels far below what free markets would generate. The results are higher-than-expected prices and slower-than-expected uptake of new biotech drugs.

In other words, the biotech drug prices in our sample appear to be inefficiently high rather than, as usually happens with price controls, inefficiently low. This has several adverse effects. First, many patients who would benefit from these extraordinary drugs are priced out of the market (where the "market" is understood to work primarily through government demand rather than private demand). Second, slower uptake of new drugs retards the accumulation of valuable information from clinical experience, which in turn can support new or expanded uses while also providing new safety information. Finally, the reluctance of the wealthiest nations outside the U.S. to make quicker use of biotech drugs reduces the expected payoffs from innovative new drugs and therefore retards research and development. This adverse effect, like the others, is likely to grow. The political forces at work in the United States are likely to gain rather than lose strength. At the same time, biotechnology-based science will create an ever larger share of new drugs, presumably generating similar pricing trends (at least until competition among similar biotech drugs leads to lower prices, which may happen fairly soon in some therapeutic areas).

We emphasize, however, that this is one case in which the undermining of research incentives through price disparities does not involve free-riding. Nations that avoid using breakthrough drugs do not reap the benefits of those drugs, at least not in the short run.

A note on direct-to-consumer information from manufacturers

One factor in the market for highly innovative drugs, especially biotechnology drugs, can easily escape notice. In the United States, manufacturers can advertise directly to consumers.

This tool could enable a manufacturer of a powerful new cancer drug, for example, to appeal directly to patients if their health care providers fail to adopt the new drug. This cannot be done in other OECD nations, all of which except New Zealand prohibit direct-to-consumer advertising (Hoek, Gendall, and Calfee 2004). The absence of DTC advertising may be one reason for the slow uptake of several very innovative drugs in the nations we studied.

7. Conclusions

In our study of 43 drugs, prescription drug prices in several wealthy nations (Australia, Canada, France, Germany, and the U.K.) were much lower than in the U.S. on average, well below relative per capita GDP. There was relatively little difference among the five foreign nations even after taking into account a 16% government-mandated rebate in Germany. All this is consistent with previous research. Separating less-unique from more-unique drugs, however, revealed important new findings. Relative prices for less-unique drugs, which are subject to strong competition, were at about half the U.S. level. This presumably reflects the exercise of monopsony power that does not exist in the U.S. where buyers as well as sellers compete. On the other hand, relative prices for highly unique drugs tended to be approximately proportional to per capita GDP or higher. Remarkably, biotech drugs were priced at or above U.S. levels in Canada and France.

These results carry uneasy implications for the future of pharmaceutical research. Contrary to what is often assumed, the same follow-on drugs that make therapeutic classes competitive also amplify incentives to conduct new R&D within these classes as R&D incentives for pioneer brands decline into non-existence with the approach of patent expiration. Our results suggest that price controls operate to blunt these incentives for follow-on drug research, leaving most of the burden to U.S. purchasers. Because these follow-on R&D results are often extremely valuable, the implications merit substantial concern.

In contrast, biotech drug prices in foreign nations appear to be above profit-maximizing levels, presumably because of political forces in the U.S., while revenues, as one would expect, are very low. This, too, undermines research incentives, mainly in connection with the creation of the most innovative kinds of drugs.

Appendix 1: Molecules Analyzed in this Study

All Molecules

Generic Name	Brand Name	Therapeutic Class
alendronic acid	Fosamax	Osteoporosis (biphosphonate)
amlodipine besylate	Norvasc	Antihypertensive
aripiprazole	Abilify	Antipsychotic
atorvastatin	Lipitor	Statin
azithromycin	Zithromax	Antibiotic
celecoxib	Celebrex	Cox-2
cetirizine	Zyrtec	Antihistamine
citalopram	Celexa	SSRI/SNRI
clopidogrel	Plavix	Anticoagulant
darbepoetin alfa	Aranesp*	Anemia
docetaxel	Taxotere	Cancer
donepezil	Aricept	Alzheimer's
enoxaparin sodium	Lovenox	Antithrombotic
epoetin alfa	Epogen*	Anemia
escitalopram oxalate	Lexapro	SSRI/SNRI
esomeprazole	Nexium	Proton Pump Inhibitor
etanercept	Enbrel*	RA/anti-TNF
fexofenadine	Allegra	Antihistamine
filgrastim	Neupogen*	White blood cell prod.
gabapentin	Neurontin	Anticonvulsant
infliximab	Remicade*	RA/anti-TNF
lamotrigine	Lamictal	Anticonvulsant
lansoprazole	Prevacid	Proton Pump Inhibitor
levofloxacin	Levaquin	Antibiotic
montelukast	Singulair	Antihistamine
olanzapine	Zyprexa	Antipsychotic
ondansetron	Zofran	Anti-nausea

Generic Name	Brand Name	Therapeutic Class
pantoprazole	Protonix	Proton Pump Inhibitor
pegfilgrastim	Neulasta*	White blood cell prod.
pioglitazone	Actos	Type-2 Diabetes
pravastatin	Pravachol	Statin
quetiapine	Seroquel	Antipsychotic
rabeprazole	Aciphex	Proton Pump Inhibitor
risperidone	Risperdal	Antipsychotic
rituximab	Rituxan*	Cancer
rosiglitazone	Avandia	Type-2 Diabetes
sertraline	Zoloft	SSRI/SNRI
sildenafil	Viagra	ED
simvastatin	Zocor	Statin
sumatriptan	Imitrex	Triptan (migraines)
topiramate	Topamax	Anticonvulsant
venlafaxine	Effexor	SSRI/SNRI
zolpidem	Ambien	Sedative/hypnotic (insomnia)

* designates a biotechnology drug, according to the Biotechnology Industry Organization

Degree of Uniqueness = Zero

Generic Name	Brand Name	Therapeutic Class
fexofenadine	Allegra	Antihistamine
cetirizine	Zyrtec	Antihistamine
amlodipine besylate	Norvasc	Antihypertensive
ondansetron	Zofran	Anti-nausea
pantoprazole	Protonix	Proton Pump Inhibitor
rabeprazole	Aciphex	Proton Pump Inhibitor
lansoprazole	Prevacid	Proton Pump Inhibitor
esomeprazole	Nexium	Proton Pump Inhibitor
simvastatin	Zocor	Statin
atorvastatin	Lipitor	Statin
pravastatin	Pravachol	Statin
sumatriptan	Imitrex	Triptan (migraines)

Degree of Uniqueness = One

Generic Name	Brand Name	Therapeutic Class
montelukast	Singulair	Antiasthmatic/allergy
levofloxacin	Levaquin	Antibiotic (fluoroquinolone)
azithromycin	Zithromax	Antibiotic (macrolide)
enoxaparin sodium	Lovenox	Anticoagulant
lamotrigine	Lamictal	Anticonvulsant
gabapentin	Neurontin	Anticonvulsant
topiramate	Topamax	Anticonvulsant
clopidogrel	Plavix	Antiplatelet
quetiapine	Seroquel	Antipsychotic
risperidone	Risperdal	Antipsychotic
olanzapine	Zyprexa	Antipsychotic
aripiprazole	Abilify	Antipsychotic
zolpidem	Ambien	Sedative/hypnotic (insomnia)
sertraline	Zoloft	SSRI
venlafaxine	Effexor	SSRI/SNRI
escitalopram oxalate	Lexapro	SSRI
citalopram	Celexa	SSRI
alendronic acid	Fosamax	Osteoporosis (bisphosphonate)

Degree of Uniqueness Two

Generic Name	Brand Name	Therapeutic Class
darbepoetin alfa	Aranesp*	Anemia
epoetin alfa	Epogen*	Anemia
donepezil	Aricept	Alzheimer's
docetaxel	Taxotere	Cancer
rituximab	Rituxan*	Cancer
celecoxib	Celebrex	Cox-2
infliximab	Remicade*	RA/anti-TNF
etanercept	Enbrel*	RA/anti-TNF
pioglitazone	Actos	Type-2 Diabetes
rosiglitazone	Avandia	Type-2 Diabetes
filgrastim	Neupogen*	White blood cell prod.
pegfilgrastim	Neulasta*	White blood cell prod.
sildenafil	Viagra	ED

* designates a biotechnology drug, according to the Biotechnology Industry Organization

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