THE LIFE CYCLE OF PHARMACEUTICALS: A CROSS-NATIONAL PERSPECTIVE

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EXECUTIVE SUMMARY

This study provides a life cycle perspective on cross-national differences in pharmaceutical prices, volumes and expenditures. Most previous studies have focused solely on cross-national differences in drug prices, comparing prices for a small sample of branded products at a single point in time. However, policymakers are increasingly concerned with total drug expenditures, which reflect volume and average prices for all products. Similarly, the pharmaceutical industry, in making decisions about pricing and launch of a drug in different countries, is concerned not only with launch price but also with the total life cycle profile of price, volume and lifetime return on investment. Globally, both policymakers and industry should be concerned with the relative contributions of different countries to the common costs of pharmaceutical research and development (R&D). These relative contributions depend not only on relative prices but also on per capita consumption and hence total expenditures.

The life cycle price, volume and expenditure profiles reported here address some of these policy and corporate questions, while also making a contribution to the methodology of cross-national comparisons for medicines.

In this study we use comprehensive data on outpatient sales for all drugs in seven countries (Canada, France, Germany,[1] Italy, Japan, the UK, and the US) for the period 1981-1992 to provide cross-national comparisons of the profiles for average price, per capita volume and expenditure over the life of a molecule. Since our price data are at the manufacturer level, our measures can be interpreted as per capita expenditure on pharmaceuticals from the payer's perspective or per capita revenue from the manufacturer's perspective. The life cycle expenditure profiles are also converted to a discounted present value at launch, which provides a rough summary measure of each country's per capita contribution to the common costs of R&D.

Although the concepts of this analysis are simple, implementation of cross-national comparisons for pharmaceuticals is complex because

1 Germany here refers to former West Germany.

of the great variety of compounds, products and presentations within and across countries. Our analysis focuses primarily on 'global' molecules, defined as molecules that are available in all seven countries. Because these global molecules are less than one third of all the molecules available in each country, we also report results for a larger sample of each country's 'US-matched molecules,' defined as molecules that are available in that comparison country and in the US. Some results are also reported for molecules that are available in the comparison country but not in the US ('local molecules'), since these are an important component of total pharmaceutical expenditures in some countries.

There were 196 global molecules in 1992, with 15-46 at each molecule age. The economic life of a molecule may last 30 years or more. However, with our sales data for nine years of the period 1981-1992 we have sales information for at most nine ages for each molecule. We therefore construct 'synthetic' age profiles based on the drugs observed at each age during our sample period. Specifically, using the molecule as the unit of analysis, we construct age profiles for each country for mean and median price per standard unit and per gram; number of units and grams consumed per capita; and per capita expenditures or revenues. We report the discounted present value of life cycle per capita revenue for a 12 year life, which corresponds roughly to life under patent protection, and for a 30 year life, which includes post-patent experience.

Results are reported in US dollars, using two alternative measures to convert local currency to US dollars. The measures that use current exchange rates at the date of sale provide a measure of the revenues that would accrue to a manufacturer in US dollars. The measures that use the exchange rate that prevailed at the date of molecule launch net out the effects of post launch exchange rate fluctuations, to provide an indicator of life cycle price and revenue profiles in the local currency units of each country.

The age-volume profiles follow an inverted U. Annual volume sold per molecule increases for the first decade after launch in all coun-

tries, reflecting the rate of diffusion of new drugs after launch. Diffusion is particularly rapid in France, Canada and the US, while diffusion is slower in Germany and the UK. Experience in the second decade after launch reflects post-patent experience and patients switching to newer molecules. Per capita volume remains relatively high in France and Canada; in Germany and the UK volume continues to increase, whereas volume levels off and declines in the US. The UK has the lowest mean per capita volume at early ages but among the highest per capita volume at older ages, indicating slow diffusion and conservative prescribing in the UK, compared to other countries.

Although Italy, Japan, Germany and France are generally viewed as having very high per capita drug consumption in aggregate, these countries do not have abnormally high consumption of the global molecules, with the exception of France (and possibly Japan, for which the outpatient sales data used here are a smaller fraction of total sales than for other countries). Thus to the extent that total drug consumption is relatively high in Italy and Germany, this reflects a relatively large number and high per capita consumption of local and other lesser molecules rather than high consumption of global molecules.

For prices, the means show the US having the highest launch prices, followed by Germany and the UK, with France lowest. However, there is wide dispersion of individual molecule prices around these means, such that the differences between countries' means are not statistically significant at conventional levels. By age 12 (i.e. by the time a molecule has been on the market 12 years), US prices are generally higher than other countries, using either mean or median price per standard unit (PSU), but the standard deviation for PSU is also higher in the US than elsewhere. For all countries, the mean and median values for real price (adjusted for GDP inflation) decline over the life cycle. This decline is generally less in local currency than when prices are measured in dollars, because the dollar measures also reflect post-launch exchange rate changes.

The life cycle profiles in per capita revenue also generally follow an inverted U, but with differences across countries that reflect their dif-

ferent price and volume profiles. Per capita revenues continue to increase in the US and Canada from age five through age 10, but in other countries per capita revenue starts to decline around age five, because the decline in prices more than offsets the continued increase in volume. The US has consistently higher mean revenues per capita than other countries from age 10 onward, because mean US prices decline less steeply with age than in other countries. However, the US differential is smaller for median values than for mean values, indicating that 'block buster' molecules have a relatively greater impact on the mean in the US. The US differential is also smaller using launch date exchange rates than sales date exchange rates. This implies that at least some of the decline in sales measured in US dollars for non-US countries reflects exchange rate movements in their currencies relative to the dollar, rather than pure domestic price declines.

The country rankings for life cycle revenue per capita are quite different than for the usual single point-in-time price level comparisons. Whereas France has the lowest 1992 price level relative to the US (30 to 58 percent lower, depending on the weights used), in terms of 12-year per capita life cycle revenues France, Canada and Italy are 96 percent of US values (using a 10 percent discount rate). Comparing 30-year per capita life cycle revenues, France ranks second, at 94 percent of the US (using a 10 percent discount rate), followed by Canada at 91 percent and Italy at 86 percent. The UK ranks lowest or second lowest in life cycle revenues. Although Germany has relatively high prices, Germany rivals the UK for bottom place in terms of per capita revenues per molecule. Revenues in Germany are only 55-58 percent of US levels for the first 12 years; German sales rise to 62-66 percent of US sales for the full 30 years, with the increase reflecting the higher per capita consumption of older molecules in Germany than in the US.

For all countries, per capita revenue is highest for global molecules, confirming that these widely diffused molecules are relatively valuable drugs. For most countries, their US-matched molecules generally have higher per capita revenue than their local molecules. The excep-

tions are France and, to a lesser extent, Germany, where mean per capita revenue for local molecules exceeds per capita revenue for US-matched molecules for some molecule age ranges, depending on the discount and exchange rates used. This confirms that the relatively high per capita expenditure on drugs in France and Germany partly reflects the large number of local molecules and the high expenditure per local molecule, rather than high expenditure on global molecules. Per capita expenditure on local molecules is lowest in the UK and the US ('local molecules' for the US are defined as molecules that are available in the US but not in Germany, which has the most molecules of all seven countries). Thus the UK and the US are similar in focusing more of their total drug spending on globally diffused molecules, which are more likely to be of relatively high clinical value, assuming that broad diffusion and high sales are indicators of relatively high clinical value.

The estimates of discounted present value of lifetime expenditure per capita for the average molecule provide a rough measure of discounted lifetime gross revenues to manufacturers in different countries. These estimates also provide a very rough measure of the per capita contribution of different countries to the common costs of R&D. However, we draw no conclusions – and none should be drawn – on the appropriateness of each country's contribution, because identifying appropriate contributions is a complex issue that is beyond the scope of this paper and because our measures are imperfect, due to the limitations of the data.

In reviewing these estimates, the following limitations of the data, should be borne in mind:

- First, our expenditure measures correspond to gross, not net, revenues to manufacturers – they do not net out costs, which may differ across countries;
- Second, the market and regulatory environment has changed in most countries since the period of our data, hence life cycle profiles and relative revenues across countries may have changed;

- Third, our estimates of revenues for the molecule overstate life cycle revenues for originator products in countries where generics capture significant market share, notably the US, the UK, Canada and Germany;
- Fourth, our estimates of prices and manufacturer revenues are upward biased in the UK and the US, because the price data do not reflect manufacturer discounts given to pharmacists in the UK and to managed care and public purchasers in the US;
- Finally, our results focus on average price, volume and revenue across molecules. In fact the experience of each molecule is different, with significant variation around the average.

Despite these limitations, this study uses more comprehensive data and provides more comprehensive evidence than previous studies of cross-national comparisons. Life-cycle sales profiles have previously been reported only for the US (Grabowski and Vernon, 1990). This study extends this approach to other countries and shows the contribution to the overall sales profiles of price and volume components.

The results here clearly demonstrate significant cross-national differences in life cycle profiles of price, per capita volume and expenditures, with important differences between global and local products. The estimates of discounted life cycle revenue per capita suggest different rankings of countries than the more common comparisons based solely on prices in a single year. Thus these findings should contribute to thinking about cross-national differences for policy purposes and for corporate decision-making.

1 INTRODUCTION[2]

Cross-national price comparisons are increasingly being used by governments as a benchmark for regulating pharmaceutical prices, at launch and over the life cycle. Italy, Canada, the Netherlands, Denmark, Spain and many other countries regulate their domestic prices based on prices in other countries. Similar proposals have been made for the US. For example, President Clinton's Health Security Act (1993) proposed using the lowest price in a group of over 20 countries as a benchmark for regulating new product prices. International price comparisons are also used informally, as one benchmark to evaluate the regulatory regimes, in many other countries, including the UK and Japan.

Previous international comparisons have focused on the comparison of prices at a single point in time, usually using a small sample of leading branded drugs.[3] However, if such comparisons are to be used for setting prices either at launch or later in a product's life, then a life cycle perspective is more appropriate, since the economic life of innovative drugs may exceed 30 years and the age-price profiles differ greatly across countries.

From the policy perspective of measuring cross-national differences in drug prices on average, the differences in age-price profiles imply that point-in-time price comparisons that use small samples may be seriously biased if based on a sample of drugs that is not representative of drugs at all ages. For example, the US GAO (1992) concluded that US prices were over 30 percent higher than Canadian prices, based on a sample of only 72 branded products. But Danzon and Chao (2000a) using comprehensive data on drug sales in 1992 found essentially no difference between Canadian and US prices at

2 This study was supported by a grant from Pfizer Inc. to the University of Pennsylvania for the study of international price comparisons for pharmaceuticals. The data were provided by IMS. The views expressed here are those of the authors and are not necessarily shared by the research sponsors.

3 For example, BEUC (1989); US GAO (1992, 1994); US House of Representatives Minority Staff (1998).

that time. The broader age mix in the latter study was one factor contributing to these very different conclusions.[4] Similarly, Berndt et al. (1993) show that measures of drug price inflation reported by the US Bureau of Labor Statistics were significantly upward biased, in part due to sampling from a limited age range of drugs.

From a social welfare perspective, optimal price differentials across countries should be based on Ramsey pricing principles (Ramsey, 1927; Baumol and Bradford, 1970). Ramsey pricing principles address the question of optimal price variation across consumer groups who all benefit from a common resource with joint costs, such as electricity generating capacity. These principles are appropriately applied to paying for pharmaceutical R&D, since the costs of drug discovery, development and proof of safety and efficacy are largely joint costs that benefit consumers in all countries (Danzon, 1997a,b). Optimal price differentials and country-specific contributions to these common costs depend on the full life cycle demand structure in different countries.

The purpose of this paper is to present evidence on cross-national differences in the life cycle profiles of pharmaceutical prices, volume of units sold and expenditures for seven major pharmaceutical markets: Canada, France, Germany, Italy, Japan, the UK and the US. Volume is normalized by population to yield a measure of per capita consumption that is independent of overall market size. We also report the mean revenue per molecule in different countries over the entire life cycle, in terms of discounted present value as of the date of launch, using alternative discount rates. These lifetime revenue estimates provide a better measure of the relative contribution of different countries to the common costs of research and development (R&D), than do the single point-in-time price comparisons reported in previous studies. However, determining optimal relative contributions to R&D costs and whether the actual contributions are roughly optimal are beyond the scope of this study.

4 Other factors contributing to the difference were the US GAO (1992)'s exclusion of all generics and use of an unweighted average of prices, rather than a weighted mean.

Differences in market and regulatory conditions are expected to contribute to significant differences in the life cycle price and volume experience of drugs in different countries, in addition to medical norms. In the US, in the 1980s prices often rose in the early years after launch of a new drug, plausibly reflecting penetration pricing strategies (Lu and Comanor, 1994; Reekie, 1978). After patent expiry, aggressive generic entry and price competition led originator brands to adopt a market segmentation strategy. Rather than compete on price, the originator brand usually abandons the price sensitive market to generics, raising the brand price to the more price inelastic, brand loyal market segment. However, the average price of the molecule (volume-weighted average across products) could fall, depending on the generic share.

In fact, post-patent generic erosion of brand market share accelerated in the US in the late 1980s, following the Waxman Hatch Act, which lowered the regulatory requirements for generic entry. The growth of managed pharmacy benefit plans, with strong generic substitution policies, accelerated this trend in the 1990s. Thus major brand products typically lose 60 percent or more of the market to generics within the first year of patent expiration. Despite a reduction in the weighted average molecule price after patent expiration, Caves et al. (1991) found no increase in total unit volume for the molecule, possibly because the effect of the lower generic price is offset by the reduction in promotion by brand manufacturers. Thus in the US, market characteristics and returns to the originator change drastically at patent expiration.

By contrast, in countries such as France, Italy and Japan, regulation of prices or reimbursement leads to a steady downward trend in real (inflation adjusted) prices after launch, mitigated possibly by the introduction of line extensions or new dosage forms of the molecule that qualify for a higher price (Ikegami et al., 1994; Danzon and Chao, 2000b). Generic entry and generic market shares after patent expiration are very small in these countries, plausibly because of little profit potential in the face of price insensitive demand and low oper-

ating margins on brand products by the time of patent expiration. Markets in the UK, Canada and Germany are more like the US, in that generics enter and gain significant market share after patent expiry; however, price competition is less intense than in the US (Danzon and Chao, 2000b, c) and originator products retain a larger market share relative to generics.

The data used in this analysis of life cycle profiles are drawn from comprehensive IMS data on all pharmaceutical sales through retail pharmacies at manufacturer prices, during the period October 1981-September 1992, excluding 1985 and 1987. We use these data to construct a mean and median price, per capita volume and expenditure (or revenue) for the sample of drugs observed at each molecule age, defined as years since launch. This provides data on sales experience at each age in a drug's life cycle, which we use to calculate the present value of lifetime revenue.

Our unit of analysis is the molecule or active ingredient, including all products in that molecule, regardless of manufacturer, because the database does not distinguish originator, licensee and generic products. Because our molecule sales estimates include sales that accrue to generics, our revenue estimates overstate revenues to originator firms in countries with significant generic market shares, such as the UK, the US, Germany and Canada. Since revenues while on patent accrue primarily to originator firms, we report a discounted present value of lifetime revenues through to age 12, as a rough estimate of patent life, in addition to 30-year life cycle estimates. The 12-year life estimates can be interpreted as representing originator returns assuming total generic erosion after patent expiry. For the 30-year life, discounting mitigates the potential bias in cross-country comparisons due to differences in post-patent generic shares. We report the average number of manufacturers per compound at different ages for each country, to provide some evidence on the role of licensees and generics.

Having data on the full universe of sales enables us to provide evidence on some of the important differences in the types of drugs available in different countries, their market shares and characteristics.

Our main focus is on 'global molecules,' defined as molecules that are available in all seven countries studied. Because these are fewer than one third of the molecules in each country, we also report some comparisons based on each country's 'US matched molecules,' which comprise all the molecules that are available in that country and the US, and on its 'local molecules,' defined as molecules that are available in that country but not in the US. The differences between life cycle profiles for global drugs and local drugs provide some insights into the importance of local products in different markets and are suggestive of different regulatory treatment of local and global products in some countries.

The data used in this study have several limitations for purposes of calculating net returns to innovation. In particular, the data do not report costs and do not distinguish originator from generic manufacturers. Nevertheless, these data are far more comprehensive and hence provide more detailed and robust evidence than previous studies of cross-national comparisons. Life cycle sales profiles have previously been reported only for the US and only for aggregate sales (Grabowski and Vernon, 1990). Our study extends this approach to other countries and shows the contribution to the overall sales profiles of price and volume components respectively. It also shows the differences between global and local products. The estimates of discounted life cycle revenue per capita suggest a different approach to international comparisons and different rankings of countries than the more common comparisons based solely on prices in a single year.

2 DATA AND METHODS

2.1 Sample

The data used in this study are from a comprehensive IMS database of pharmaceutical sales in seven countries for the period October 1981 through to September 1992, excluding 1985 and 1987 which were omitted due to the complexity and cost of data acquisition. Our analysis focuses on single molecule drugs. We exclude combination (multiple molecule) products because the mix of ingredients is not uniform across countries and because the price for the combination cannot be accurately allocated to the separate molecules.[5]

Our analysis is based on sales through pharmacies, which account for over 80 percent of sales in most countries. Data on sales to hospitals were unavailable for some countries, and for other countries the reported price data may be inaccurate because of undisclosed discounts.[6] Excluding sales to hospitals should not lead to significant bias in cross-national comparisons for most countries which have similar hospital shares, at 12-20 percent of total sales. The exception is Japan, where drug sales through hospitals are 52 percent of total sales reported by IMS. Because these omitted hospital sales include the outpatient care that is delivered in the outpatient departments of large public hospitals and physician-operated clinics, our data on outpatient sales in Japan are downward biased. The sales totals for the US are also downward biased because the IMS data do not capture sales through health maintenance organization- (HMO-) owned pharmacies, supermarkets and mail order, which together were estimated at 19 percent of total sales including hospitals and retail pharmacies (US Congress OTA, 1993, p.20).

We exclude from the sample products with sales of less than 1,000 packs and 1 kilogram of active ingredient, to reduce sampling error.

5 Another reason for excluding multiple molecule products is that many are over-the-counter products with relatively little research content, hence are less relevant to this analysis.

6 Sales to hospitals are often at discounted prices, even in countries that regulate retail drug prices such as France. Such discounts are not fully captured in the IMS data.

We have also excluded a small number of outlier observations, defined as molecules for which the recorded change in price between successive years was implausibly large, defined as a multiple greater than three or less than one third. These observations are excluded only for the years in which the extreme changes occur.

Our sample includes both prescription and over-the-counter (OTC) sales for the drugs included. Our data do not identify OTC packs. However, even if it were possible, it would not be appropriate to exclude the OTC packs for our molecules. In some cases, the OTC packs result from a prescription-only to OTC 'switch' in the status of the medicine – for example, for ibuprofen – and both the prescription and OTC forms may continue to be sold. However, our sample selection criteria should exclude products that are primarily OTC. The focus on single molecule products excludes combination products that are more likely to be OTC consumer products rather than research-based pharmaceuticals. Further, we exclude from the global and US-matched samples all molecules with no identified originator product in any of the relevant countries, using information on originator status which we have for the US and Germany in 1992.

2.2 Global, US-Matched and Local Molecules

Most of our analysis focuses on global molecules, defined as molecules that were marketed in all of the seven countries in at least one year of the observation period. A reasonable presumption is that molecules with broad international diffusion are of relatively high therapeutic value. Manufacturers have incentives to launch a drug in any country where the expected revenues are at least equal to the country-specific marginal costs, including the costs of meeting regulatory requirements for proof of safety and efficacy. Thus drugs that are local-only are more likely to have weak evidence of efficacy or low potential market value.

Since global molecules account for less than one third of the total number of molecules available in each country, some results are also

reported for two other samples. For each country, the sample of US-matched molecules comprises molecules that are available in both the comparison country and the US in at least one year. These US-matched samples are larger than the global sample, but the additional molecules are not identical across countries. The US-matched samples are also likely to consist of drugs with relatively high therapeutic value, since the US is widely viewed as a relatively profitable market that most drugs would seek to enter if the high and costly US regulatory requirements for proof of efficacy could be met.

The local sample for each country is the complement of that country's US-matched sample, that is, it includes molecules that are available in that country's domestic market but not in the US. Local drugs, which account for over 40 percent of sales in some countries, differ across countries and are often produced by local firms. Local drugs are presumably of less proven therapeutic value than the global or US-matched samples, assuming that any drug would be brought to the US if it could meet the Food and Drug Administration (FDA) requirements and be expected to generate enough revenue to cover these and other costs of launch in the US. Thus per capita expenditure on local drugs, compared to global or US-matched drugs, provides some measure of how different countries allocate their total drug spending across these different types of drugs. It also shows that countries can have high expenditures in aggregate but relatively low expenditures on the global drugs that are of interest to multinational companies.

2.3 Launch Dates and Product Age

Since the data on molecule launch dates in each country are incomplete, we estimate molecule age based on the earliest reported product launch date in each country. Specifically, we define the launch of molecule i in country j, $LAUNCH_{ij}$, as the earliest reported launch date of any product in molecule i in country j. Molecules for which all products have missing launch dates are excluded from the analysis. The age of molecule i in country j in year t is defined as the number

of years since launch: $AGE_{ijt} = t - LAUNCH_{ij}$.[7] Our estimate of molecule age is thus a country-specific measure – that is, the age of molecule i in year t could differ across countries – rather than an absolute estimate of molecule age relative to the first launch in any country worldwide, as would be required to incorporate lags in launch into lifetime revenue estimates. The data on patent expiration date were too incomplete to be useful. We use 12 years as an estimate of market life under patent, which is reasonably consistent with the observed trends in sales, but recognize that this is only approximate.

2.4 Constructing a Synthetic Life Cycle

Our 1981-1992 data, omitting 1985 and 1987, provide sales figures for up to nine years in the economic life of each molecule. Not all drugs are observed for the full nine years, due to entry and exit, as well as sampling variation. Since the economic life may extend for 30 years or more, we use the observations on molecules at different stages of their life cycles to construct a synthetic life cycle profile of 30 years of sales for each country. Our observation period implies that sales experience at ages 0-11 is based on molecules launched between 1970 and 1992; experience at ages 12-22 is for molecules launched between 1959 and 1980; and experience at ages greater than 22 is for molecules launched before 1970. This approach combines the early life experience of recently launched drugs with the experience of older drugs at later ages.

7 The reported product launch dates do not necessarily correspond to observed sales. For example, for molecules with first reported product launch dates between 1981 and 1992, the mean lag between reported product launch date and first observed sales is almost two years for most countries; median lags are less, because the distribution of lags is positively skewed. This lag could reflect early sales that are either to hospitals or are too small in volume to be recorded or to meet our minimum sales screens; real lags between regulatory approval and product launch, possibly because of lags in obtaining price approval for reimbursement; or reporting error.

The alternative, in theory, would be to use the full life cycle experience for a given cohort of molecules. Even if such data were available, this approach would have the disadvantage that the youngest ages – which are most critical in present value calculations – would reflect early sales of drugs launched in the late 1960s and early 1970s. Since both the market environment and the types of drugs were very different then than in the 1990s or today, this approach would almost certainly yield a worse predictor of current and future experience than our approach, which includes the early age experience of drugs launched through to 1992. A potential disadvantage of our approach of using the experience of different drug cohorts is that the age-specific experience may be confounded by cohort effects. Although drugs launched in different time periods embody different technologies, such technology-related cohort effects are common across countries and so should not introduce systematic cross-country bias.

Obviously, this analysis based on data from 1981-1992 is not necessarily accurate for current experience of prices and volumes, because regulatory and reimbursement environments have changed, as have medical norms and available therapies. Competitive pressures on prices and per capita volumes have increased in the US in recent years, while regulatory pressures have increased in other countries. Nevertheless, many of the main country-specific characteristics are probably still valid, as are the basic conclusions related to methodology and policy. Where more recent experience is known to be different from that shown in the data here, this is noted.

More fundamentally, our study illustrates the dilemma facing any analysis of life cycle returns: given the long economic life of medicines, there is an inevitable trade-off between using current data, to reflect current drugs and pricing environments, and having a long experience profile for a single cohort of drugs. Our approach, using the experience of different cohorts from the same 11-year time period, is a compromise.

2.5 Units of Volume and Price

Our unit of analysis is the molecule or active ingredient, such as ranitidine, cimetidine, and nifedipine. A given molecule may be sold as different products with different manufacturers, including licensees and generic producers. The term 'product' here thus refers to manufacturer within molecule – for example, Bayer aspirin is one product in the molecule aspirin. Using the molecule as the unit of analysis, sales for the molecule in a particular country-year are calculated as the sum of sales of all products in that molecule in the country-year, regardless of manufacturer, dosage form, strength or pack size. This is equivalent to assuming that 'a pill is a pill', regardless of possible differences between different products in the same molecule due, for example, to inactive ingredients. We use the molecule because our data do not identify originator versus licensee or generic products, and because the sample of products with consistent data across ages was too small for reliable estimates.

Each molecule is typically available in several different dosage forms, strengths and pack sizes, all of which differ across countries. This creates a problem of defining a common unit of volume that is both homogeneous and generally applicable. We use two measures of volume, the number of IMS standard units (SU) and number of grams of active ingredient (KG). A standard unit is defined by IMS as one tablet, one capsule, five milliliters of a liquid, etc. It is intended as a rough proxy for a dose, recognizing that this is an approximation.[8] Important for our purposes is that systematic differences across countries in strength per standard unit may influence price and volume. Our second measure is number of grams of active ingredient. The advantage of these two measures – SU and grams – is that they are reported for all dosage forms, hence they are the only two available common units of measure that permit aggregation over different

8 The standard unit may be an imprecise measure of a dose for inhalers, topical applications, etc., and this contributes to some extreme values in our measures of price.

forms, strengths and packs of each molecule and over different molecules.[9] More fundamentally, there is no meaningful homogeneous unit for drugs that have very different therapeutic effects, or even for a given drug for which prescribing habits differ across countries.[10] Thus measures of volume – standard units and grams – are an admittedly imperfect approach to a problem that has no perfect solution.

Price per standard unit and price per gram, by molecule age and country, are defined for each molecule by dividing total expenditures by number of units or grams. The price for each molecule is thus a volume-weighted average over all forms of all products in the molecule. The distribution of prices across molecules has more extreme values for grams than for standard units, hence mean price per gram is more unstable across ages, as the sample of molecules changes. The price analysis here therefore focuses on price per standard unit rather than price per gram. Because these extreme values can significantly influence the mean values, medians are also reported as an alternative measure of central tendency.

2.6 Exchange Rate Adjustment

When we measure foreign age-price profiles in US dollars, the observed changes in prices can reflect changes in the foreign currency-US dollar exchange rate, in addition to changes in prices in the local currency. We use two approaches to convert foreign currency values to constant 1992 US dollars, in order to distinguish true life cycle

9 The WHO defined daily dose (DDD) system (grams of active ingredient per day) provides alternative units for measuring drug consumption. But DDDs for different molecules within a therapeutic class are not defined to achieve a standardized effect, and aggregating DDDs across therapeutic categories suffers from the same heterogeneity issues as standard units or grams. Danzon (1996) discusses an approach to defining standardized (potency-equivalent) daily doses.

10 For example, strength per dose is systematically weaker in Japan than in other countries, in part because of the practice of typically prescribing several drugs to be taken simultaneously.

price changes from exchange rate fluctuations (algebraic formulations for these approaches are provided in the Appendix to this monograph):

a. *Sales Year Exchange Rates.* This approach converts foreign currency sales to US dollars in the year the sales occurred, using the prevailing quarterly exchange rates, as reported by IMS. We then use the US GDP deflator to adjust dollar values from year t to constant 1992 dollars. This approach approximates the revenues that a US firm could earn from foreign sales, assuming immediate conversion of foreign currency sales to US dollars, no currency hedging and no taxes. Using these sales date exchange rates, our life cycle price profiles in countries other than the US reflect changes in the exchange rate of that country's currency relative to the US dollar, in addition to the life cycle price change in local currency terms. For example, if the yen price of drugs in Japan declines between age 1 and age 4 of the life cycle, but the yen appreciates relative to the dollar over the same period, we could observe no change in dollar prices but this would mask a real life cycle price change in local currency terms.

b. *Launch Date Exchange Rates.* The second approach converts foreign currency values to US dollars at the exchange rate prevailing at the date of molecule launch in the foreign country, regardless of the calendar year in which the sales occurred. The dollar value of sales in a given year is then adjusted to constant 1992 dollars using the US GDP deflator. The result can be interpreted as the counterfactual dollar value of foreign sales had US-foreign exchange rates remained at their launch date value throughout the life cycle of the molecule. Thus the difference between the lifetime revenues using sales date and launch date exchange rates reflects the impact of currency fluctuations relative to the US dollar over the molecule's life.

2.7 Price Change over the Life Cycle in Constant Local Currency Units

The cumulative change in real prices over the life cycle in local cur-

rency units, net of country-specific general inflation, is also reported. Specifically, we first convert local currency units in year t to constant 1992 values of the local currency using the country-specific GDP deflator. We then compute one-year and cumulative indexes in constant local currency units. (See the Appendix for an algebraic explanation). These indexes show the pure cumulative change in real local prices over the life cycle, net of each country's general inflation and net of foreign exchange fluctuations.

2.8 Age-specific Expenditures, Price and Volume per Capita

All reported sales data are converted to constant 1992 US dollars, using either sales date or launch date exchange rates and US GDP inflation adjustment, as described above. For each molecule age, we compute country-specific expenditures per capita by averaging the sales for all molecules in the sample at that age in that country for any year in our observation period 1981-1992.

Similarly, volume per capita is calculated for molecules at each age in each country, by calculating the average number of units (either standard units or grams) sold for all products in all molecules with that age in that country. Each year's sales are divided by the country's population in that year, to yield per capita volume. For price, we calculate both an unweighted and a weighted mean price per unit at each age in each country. The weighted mean weights each molecule's average price by that molecule's share of total expenditures on molecules of that age in that country.

The discounted present value of lifetime revenue per capita for the average molecule in each country is the sum of the average per capita expenditures at each molecule age, with each value discounted from that age to launch. We report results using discount rates of 0, 5 and 10 percent. A zero discount rate corresponds to simply summing revenues at all ages without discounting A 10 percent discount rate is roughly equivalent to previous estimates of the real cost of capital for

pharmaceutical firms,[11] and hence is probably most relevant for the manufacturer perspective. A 5 percent rate is often used as a social discount rate, so may be more relevant for the policy perspective. These discounted values are reported for a 12-year life, which corresponds roughly to life under patent protection, and a 30-year life. Although the database reports sales for some molecules at older ages than 30, mean estimates for these older ages are less accurate because of fewer observations and less accurate launch date information for older products. Truncating the economic life at age 30 has little effect on the present value at launch, due to the effect of discounting sales at later ages.

(See the Appendix for algebraic formulations of these calculations).

2.9 Number of Manufacturers

We report the mean number of manufacturers per molecule by age for each country, to provide a measure of the number of potential competitors over the life cycle in different countries. At early ages the existence of multiple manufacturers reflects co-marketing and co-promotion licensing arrangements, which are unlikely to lead to aggressive price competition. At ages beyond patent expiration, however, the number of manufacturers presumably reflects generic entrants. Thus these measures of number of manufacturers give some sense of the extent of generic competitors at later ages.

11 DiMasi et al. (1991) estimate a beta of one for the pharmaceutical industry and a real cost of capital of 10 percent. Myers and Shyam-Sunder (1996) estimate a higher cost of capital for early stage research. Drawing on these ideas, US Congress OTA (1993) used a real average cost of capital of 11 percent.

3 LIFE CYCLE TRENDS IN VOLUME, PRICE AND REVENUES

3.1 Number of Matching Molecules

Cross-national differences in pharmaceutical markets are illustrated in Table 1, which reports the number of molecules with retail pharmacy sales in 1992 for each of the seven countries. France, Germany, Italy and Japan have more molecules than the US, despite their smaller populations. Although there are over 740 molecules in each country, only 196 are common to all seven countries and hence can be included in our global sample. By contrast, each country has over 500 molecules that match with the US. Thus the US-matched samples are significantly larger than the global samples.

Of the molecules that are available in the US, less than 60 percent are available in France, Italy, and Japan. These US-matched molecules represent less than 50 percent of all molecules that are available in these countries, whereas US-matched molecules constitute 72 percent of molecules in the UK and 85 percent of molecules in Canada. In all countries the US-matched molecules account for a larger fraction of sales than of number of molecules, confirming that these molecules are of above average sales and hence plausibly are above average in therapeutic value. Note that, with the exceptions of the UK and Canada, the molecules that are available both in the US and another country represent a greater proportion of the total molecules available in the US than of the total molecules available in the comparison country. This is further evidence in support of the hypothesis that the US market includes a disproportionate fraction of broadly diffused molecules compared to most other countries, plausibly because of relatively high FDA screens for efficacy.

3.2 Number of Global Molecules by Age

Figure 1 shows number of global molecules with sales at each age in any of the years of our 1981-1992 time period. Despite 196 global molecules in 1992, the sample size for each age is small – only 15-46 molecules – and changing across ages, which makes the life cycle pro-

Table 1 **Number of Molecules and Market Share Single Molecule Products, Retail Pharmacy, 1992**

Number of molecules[a]	**US**	**Canada**	**France**	**Germany**	**Italy**	**Japan**	**UK**
Total	963	746	1,095	1,244	1,060	1,176	830
Launched ≥1970	405	279	467	548	520	534	351
Global molecules in all 7 countries	196	196	196	196	196	196	196
Molecules matched with US	963	632	526	645	508	537	596
% of US molecules	100.0%	65.6%	54.6%	67.0%	52.8%	55.8%	61.9%
% of country's molecules	100.0%	84.7%	48.0%	51.8%	47.9%	45.7%	71.8%
Expenditures, 1992 ($millions)[a]							
Total	28,210	2,608	8,772	7,292	8,580	11,674	3,904
Molecules launched ≥ 1970	18,305	1,686	5,622	4,148	6,509	9,024	2,408
% of total	64.9%	64.7%	64.1%	56.9%	75.9%	77.3%	61.7%
Molecules matched with US	28,210	2,388	4,839	4,963	5,117	6,074	3,270
% of total	100.0%	91.6%	55.2%	68.1%	59.6%	52.0%	83.8%

Notes: Minimum volume screens applied.
a Molecules with at least one valid product launch date.

Source: Calculated from IMS data for sales through retail pharmacies, 1992.

files for all variables quite erratic. For most countries the number of molecules is relatively low at early and later ages, reaching a maximum at ages 5-12. This inverted U shaped distribution of sample size presumably partly reflects insufficient volume at early ages (0-4) for all 'young' molecules to be represented in the database, followed by peak market penetration in middle age (5-12) and a subsequent slow decline in later years after patent expiration.

Patterns of diffusion clearly differ across countries. In particular, the UK has relatively few molecules at early ages, but this pattern is

reversed at later ages. This is consistent with the conventional view that UK doctors are relatively conservative, with a high preference for older drugs due to either medical norms or financial incentives. Conversely, the US and Canada have relatively young age distributions of global molecules, with relatively large numbers at young ages but relatively small numbers at older ages.

Figure 1 suggests that the potential for selection bias due to differences in country size is not a serious factor. In theory, estimates of relative life cycle revenues could be upward biased in countries with relatively small market size if the sample at low-volume ages included only the most successful drugs, i.e. those with sufficiently large volume to be measured in the database, whereas larger markets could support more minor drugs with lower per capita sales at low-volume ages.[12] However, although Canada has the smallest population it has a relatively large number of molecules in the low-volume earlier ages, whereas the US has among the fewest molecules in the low-volume years after age 17 despite having the largest population. Thus differences in medical practice and other determinants of drug consumption appear to dominate differences in population size in determining the life cycle age distribution of molecules. Further evidence that market size bias is negligible in our countries is provided by the fact that Germany, France, Italy and Japan all have more molecules than the US (Table 1), despite the much larger US population.

12 Market size bias could in theory exist if the fixed costs of launching a drug were uniform in all countries but expected revenues were roughly proportional to population. Under these assumptions, the countries with smaller populations would have fewer molecules and only those with the highest expected sales, whereas in larger markets less valuable products could break even because the larger population size could offset low per capita sales. Although the global sample is comprised of molecules that were launched in all seven countries, the year-specific sales data that are observed could in theory be subject to this country-size selection bias at early and later ages when sales are generally low. In practice there is no evidence of such bias.

3.3 Volume-Age Profiles

Figures 2a and 2b, respectively, show volume-age profiles for mean and median number of standard units per 1,000 population, by molecule age. The life cycle inverted U profile of volume is more evident from the medians than from the mean values, which are very erratic for the post-patent years with smaller samples. Volume increases for the first decade in all countries, with particularly rapid diffusion in France, Canada and the US, while diffusion is slower in Germany and the UK. In the second decade after launch, per capita volume remains relatively high in France and Canada, Germany and the UK continue to increase, whereas volume per person levels off and declines in the US. The UK increases from having the lowest mean per capita volume at early ages to having among the highest per capita volumes at some older ages, implying slow diffusion in the UK and conservative prescribing, defined as a higher preference for older molecules relative to newer molecules, compared to other countries.

It is interesting to note that although Italy, Japan, Germany and France are generally viewed as having very high per capita drug consumption in aggregate (for example, Burstall, 1991), this conclusion does not hold for global molecules, with the exception of France. Thus, to the extent that total drug consumption is high in Italy and Germany, this appears to reflect relatively high volumes of local molecules rather than global molecules. This is consistent with the large number of local molecules in these countries (Table 1) and further evidence discussed below. For Japan, conclusions on volume are tentative because the retail sales included here omit Japan's relatively large sales through hospital outpatient departments. Thus our data yield a downward biased measure for total outpatient volume in Japan.

The volume-age profiles in Figures 2a and 2b peak later in life than the profiles for number of molecules (Figure 1). This could reflect an increase in the rate of new molecule entry. It could also reflect early withdrawal of molecules with relatively low sales, which is plausible if there are significant molecule-specific fixed costs of continuing pro-

duction and promotion. If more successful drugs do have a longer economic life, our sales estimates for older ages, which are conditional on the sample of drugs that remained on the market, may be upward biased estimates for the unconditional sales of all drugs.[13] Although the resulting estimates of life cycle revenue may be upward biased for the unconditional expectation for the average drug, cross-national comparisons are not necessarily biased, since the same bias appears to apply to all countries.

3.4 Sales-Age Profiles

Figures 3a and 3b, respectively, show mean and median sales revenue per molecule over the molecule life cycle, normalized per 1,000 population to adjust for differences in population size between countries. The terms 'sales,' 'revenues' and 'expenditures' are used interchangeably here, reflecting the fact that sales imply revenues to manufacturers and expenditures by payers/customers. For these figures, local currencies are converted to US dollars at sales date exchange rates and then converted to constant 1992 US dollars using the US GDP deflator.

For the US and Canada, sales follow an inverted U with a peak at ages 9-10, roughly corresponding to the age of patent expiration, with a rapid decline thereafter.[14] Canada's sales-age profile is very similar to that of the US, with similar maximum values per capita. For Italy, France and Japan, sales peak earlier and then trend down slowly. The UK and Germany have much flatter sales-age profiles and the post-patent decline appears to occur later and be more gradual. Recall, however, that the sales figures here are for all products in the molecule

13 In principle this could be corrected by adjusting for the probability of exit at each age, but in practice the sampling variability precludes reliable estimation of these probabilities.

14 The US life cycle revenue curve estimated here is similar to that reported in Grabowski and Vernon (1990, 1996).

and do not reveal the shifting in share from originator products to generics within the molecule, which occurs in the UK, Germany, Canada and the US after patent expiry. The peak value of mean sales per capita is over 25 percent lower in all other countries than in the US and Canada.

These differences in sales-age profiles – particularly the earlier and lower peaks and greater post-patent decline in most countries other than the US – appear to be influenced more by prices than by per capita volume. Whereas per capita revenues continue to increase in the US and Canada from age five through to age 10, in all other countries revenue declines despite flat or increasing volumes through to age 20 (see Figures 2a and 2b). This is because real prices decline in most countries, due to price increases that are less than inflation and some nominal price cuts, especially in Japan. The US has consistently higher mean and median revenue per capita than other countries from age 10 onward, although US per capita volume is not abnormally high (see Figure 2a and 2b), because during our observation period of 1981-1992 real prices in the US did not decline as steeply as in other countries. Since the early1990s, price increases in the US have been much less than in the 1980s and generic erosion of originator sales after patent expiration has been greater. Thus a study based on more recent data would probably show more rapid post-patent decline in sales revenue in the US.

These mean gross sales data overstate revenues to originator firms in countries where generics capture a significant market share after patent expiration, in particular the US, Germany, the UK and Canada. For example, for the US in the 1990s, generics often captured 60-80 percent of the market within the first 6-12 months after patent expiration.

These gross sales data further overstate revenues to originator firms in the US and the UK because the data do not net out discounts and rebates. In the US, originator firms give significant rebates and discounts to managed care and public payers, both before and after patent expiration, particularly in crowded therapeutic categories. In the UK, originator products may be discounted to pharmacists in

order to compete with parallel imports even before patent expiration. After patent expiration, both originator and generic manufacturers may compete by offering discounts to pharmacists. Because these manufacturer discounts to pharmacists are not reflected in the sales data used here, UK sales revenues are upward biased.

The difference between per capita sales in the US and other countries is generally larger if the comparison is based on means rather than median values. This greater difference in the means than the medians suggests that the impact of 'blockbuster' drugs may be greater in the US than in other countries. Grabowski and Vernon (1990) show that the distribution of sales across drugs in the US is highly right-skewed, with the top 30 percent of drugs having much higher lifetime sales than the remaining 70 percent. Although similar detailed analysis is not available for other countries, the evidence here suggests that the few blockbusters account for a smaller percent of total sales in other countries than in the US.

The differences between per capita sales in the US and other countries is less when using launch date rather than sales date exchange rates to convert other currencies to US dollars (Figure 3c). For example, using launch date exchange rates, median per capita revenue for France is similar to or greater than that for the US at several ages. The higher non-US values using launch date rather than sales date exchange rate reflects the decline in the value of other currencies relative to the US dollar during the life of the molecules in our sample.

3.5 Price Levels and Price-Age Profiles

To illustrate the trends in prices over the life cycle, Figures 4a, 4b and 4c respectively show the mean value across molecules for price per standard unit (PSU) and median values for PSU and price per gram (PKG).

The mean price across molecules by age is rather unstable, because of the small and changing sample of molecules at each age and because of some extreme outlier values, particularly for PKG. Median values

are more stable for PSU but still have some extreme values. Comparing mean PSU, the point estimates show the US having the highest launch prices, followed by Germany and the UK, with France lowest; however, given the large standard deviations, these differences are not statistically significant at conventional levels. As of age 12, US prices are generally higher than other countries,[15] using either mean or median PSU, but the standard deviation for PSU is also higher for the US, implying greater variation within the sample.

For all countries, these mean and median values suggest that real price levels decline dramatically over the life cycle. Recall, however, that the decline in price profiles with age may be overstated for all countries by cohort effects, that is if more recent molecules are typically launched at higher real launch prices than previous cohorts of molecules, due to either superior effectiveness, growth in insurance coverage or other changes over time. Further, the life cycle price profiles using sales date exchange rates are more influenced by currency fluctuations relative to the dollar for older ages than younger ages.

Table 2 reports the cumulative price change over various phases of the life cycle using a Divisia price index[16], both using sales date exchange rates and launch date exchange rates. Mean and standard deviation of PSU, and mean and median of PKG are also reported, along with sample size. The Divisia price indexes measure the cumulative percentage price change from launch to each specified age. Values greater or less than unity respectively imply price increase or decrease since launch. For example, the value of 0.66 for PSU in France for age six (sales date exchange rate) implies that, on average,

15 This ignores a few extreme values at late ages for Canada, which were influenced by a small number of extreme values that probably reflect data error and so are omitted from Figure 4b.

16 The Divisia index is a chain-weighted measure of price change. The index of price change between age t and age t+1 is the volume-weighted geometric mean of the price change between age t and t+1 for all molecules observed at those ages, where the weight for each molecule is its volume share, averaged over the two years. The cumulative index reported in Table 2 at age 6, for example, is the product of the one-year indexes for age 0 to 1, age 1 to 2, age 2 to 3, age 3 to 4, age 4 to 5 and age 5 to 6.

Table 2 **Real Price Levels and Divisia Indexes of Price Change by Age: Global Molecules**

			At Sales Date Exchange Rate[a]				Cumulative Divisia Index[b] of Real Price Changes since Launch			
			Means		Medians		At Sales Date Exchange Rate		At Launch Date Exchange Rate	
Country	Age	No. of Molecules	Unweighted PSU Mean	PSU St. Dev.	PSU	PKG	PSU	PKG	PSU	PKG
Canada	1	33	0.915	1.123	0.557	6.310	0.946	0.948	1.010	1.010
	6	41	0.395	0.318	0.297	7.720	0.960	1.070	0.840	0.930
	12	37	0.383	0.293	0.282	6.683	1.070	1.072	1.060	1.060
	20	22	0.261	0.293	0.166	3.542	1.220	1.140	1.330	1.240
	30	19	0.122	0.113	0.079	2.466	1.245	1.083	1.201	1.042
France	1	30	0.808	0.887	0.599	5.330	0.960	1.000	0.860	0.900
	6	35	0.404	0.631	0.221	3.745	0.660	0.670	0.580	0.580
	12	35	0.341	0.564	0.173	3.570	0.500	0.450	0.890	0.780
	20	33	0.189	0.201	0.101	2.836	0.290	0.280	0.560	0.530
	30	15	0.128	0.128	0.091	2.587	0.212	0.192	0.408	0.364
Germany	1	24	1.204	1.430	0.654	8.433	0.970	0.970	0.907	0.909
	6	37	0.509	0.439	0.323	5.235	0.780	0.800	0.620	0.630
	12	42	0.503	0.479	0.320	6.620	0.670	0.700	0.670	0.690
	20	27	0.295	0.430	0.137	8.520	0.340	0.340	0.200	0.200
	30	17	0.245	0.163	0.205	4.102	0.190	0.166	0.088	0.076
Italy	1	27	0.952	1.163	0.582	6.456	0.940	0.930	0.970	0.960
	6	34	0.376	0.368	0.257	4.279	0.730	0.680	0.720	0.660
	12	28	0.201	0.152	0.182	3.718	0.600	0.520	1.160	1.010
	20	21	0.169	0.135	0.123	3.543	0.520	0.440	1.790	1.508
	30	22	0.137	0.096	0.123	2.839	0.632	0.445	2.589	1.819
Japan	1	38	0.908	1.931	0.378	11.948	0.970	0.970	0.880	0.870
	6	37	0.433	0.421	0.280	10.439	0.550	0.610	0.400	0.440
	12	27	0.680	1.864	0.240	7.813	0.270	0.320	0.145	0.170
	20	30	0.351	1.113	0.114	3.495	0.130	0.140	0.045	0.060
	30	18	0.206	0.476	0.071	3.175	0.049	0.056	0.019	0.021

Table 2 **Real Price Levels and Divisia Indexes of Price Change by Age: Global Molecules** *continued*

			At Sales Date Exchange Rate[a]				Cumulative Divisia Index[b] of Real Price Changes since Launch			
			Means		Medians		At Sales Date Exchange Rate		At Launch Date Exchange Rate	
Country	Age	No. of Molecules	Unweighted PSU Mean	PSU St. Dev.	PSU	PKG	PSU	PKG	PSU	PKG
UK	1	24	1.161	1.570	0.806	8.552	0.910	0.890	0.980	0.960
	6	24	0.352	0.193	0.297	4.599	0.630	0.590	0.740	0.690
	12	33	0.465	0.985	0.219	5.294	0.420	0.380	1.010	0.920
	20	28	0.170	0.159	0.112	3.579	0.212	0.202	0.820	0.790
	30	20	0.177	0.328	0.079	1.490	0.127	0.118	0.619	0.571
US	1	37	1.400	2.562	0.519	10.278	1.030	1.020	1.030	1.020
	6	39	0.454	0.261	0.354	11.008	1.240	1.240	1.239	1.242
	12	31	0.777	1.213	0.458	5.867	1.850	1.560	1.854	1.560
	20	19	0.724	1.767	0.183	2.926	2.270	1.640	2.271	1.642
	30	15	0.294	0.491	0.138	2.973	1.821	1.325	1.820	1.330

Notes:

a Foreign currency units are converted to $US at exchange rate prevailing in the year of sales. Adjustment to constant 1992 $US using US GDP deflator.

b Divisia Index: cumulative total of annual divisia indexes.

PSU = price per standard unit.

PKG = price per gram of active compound.

real prices for molecules at age six were 66 percent of their value at launch, a decline of 34 percent.

The Divisia indexes using sales date exchange rates show a monotonic decline in real prices over the life cycle for all countries except the US and Canada, for both PSU and PKG. The decline in real prices is most dramatic in Japan, where PSU drops to 27 percent of its initial level by age 12. For the UK, the real price (PSU) at age 12 is

42 percent of the initial price, and in France it is 50 percent.

By contrast, prices in Canada slightly increase through to age 12 and beyond. In the US, real prices for these cohorts appear to increase by 56-85 percent by age 12, with continued increase through to age 20. This reflects in part the pattern of annual price increases that was the norm in the late 1980s, when drug price indexes significantly outpaced general inflation in the US, whereas in the 1990s drug prices have roughly tracked general inflation or with only 1-2 percentage point excess drug price inflation. Similarly, price increases in Canada have been much more modest in the 1990s. Thus for both the US and Canada, these price data almost certainly overstate real price growth over the life cycle for current drug cohorts. In addition, the US price profiles may be more upward biased by sample selection at later ages than in other countries. The number of molecules in the sample declines by almost half between age one and age 20 in the US, whereas for the UK, France and Germany there are actually more molecules at age 20 than at age one. If older products in the US are disproportionately the more valuable products, because less valuable molecules are more likely to be withdrawn, our estimates of price profiles and price indexes, which are conditional on molecules remaining on the market, may be upward biased for the unconditional estimate of expected value for all molecules. The US differential is also much smaller for the median than the mean price, again suggesting higher prices for older, blockbuster products in the US than in other countries.

The price profiles at sales date exchange rates provide a measure of prices that would accrue to a multinational firm based in the US. The price profiles using launch date exchange rates, reported in the last two columns of Table 2, provide a measure of price change in local currency because they use each molecule's launch date exchange rate throughout its life cycle. These measures net out currency fluctuations but may still be biased by cohort effects. For Italy, which underwent a major currency revaluation during the period of our data, the launch date exchange rate estimates are unreliable and should be disregarded. For several other countries, the real life cycle price change in local cur-

rency is less negative using launch date exchange rates than with sales date exchange rates that incorporate exchange fluctuations. For example, for PSU (second to last column in Table 2) the age 12 value of 1.01 for the UK implies that real prices were roughly flat through to age 12 in the UK. For France the decline is only 11 percent (0.89 for age 12), instead of the 50 percent using sales date exchange rates. For Japan, the launch date estimates imply an even greater decline in prices than the sale date estimates, which are upward biased by the appreciation of the yen.

3.6 Discounted Present Value of Life Cycle Revenue per Capita

Tables 3 and 4 report the present value of per capita revenues over the life cycle, in constant 1992 US dollars, at discount rates of 0 percent, 5 percent and 10 percent per annum. Present values are reported separately for the three subsamples: global molecules, US-matched molecules and local molecules. The values through to age 12 correspond roughly to sales while on patent, whereas the values through to age 30 include post-patent sales of all manufacturers, including generics. Tables 3 and 4 use sales date and launch date exchange rates, respectively, to convert other currencies to US dollars. In each table, the upper panel reports per capita dollar values, and the lower panel expresses each country's value as a ratio relative to the corresponding value for the US.

For all countries, per capita revenue is higher for global molecules than for US-matched molecules, which in turn generally have higher per capita revenue than local molecules. These findings support the hypothesis that global diffusion and, to a lesser extent, availability in the US are indicators of relatively high market value. The exceptions are France and Germany, where mean per capita revenues of local molecules exceed mean per capita revenue for US-matched molecules for the 30-year life at some discount rates. This confirms that the relatively high per capita expenditures on drugs in these countries reflect high expenditures per local molecule and the large number of local molecules shown in Table 1.

Table 3a **Mean Life Cycle Revenues Per Molecule for Global, US-Matched and Local Molecules**
Discounted Present Values, $1992 US[b], Converted to $US at Sales Date Exchange Rates[a]

US $ Per 1,000 Population										
		Global Molecules[c] Discount Rate			US-Matched Molecules Discount Rate			Local Molecules[c] Discount Rate		
Country	Age	0%	5%	10%	0%	5%	10%	0%	5%	10%
Canada	0-12	5.665	3.996	2.842	4.736	3.366	2.416	2.333	1.775	1.366
	0-30	9.419	5.448	3.402	8.112	4.665	2.915	2.746	1.978	1.462
France	0-12	5.098	3.792	2.869	4.240	3.119	2.333	3.435	2.453	1.782
	0-30	9.628	5.462	3.491	8.347	4.637	2.902	10.479	5.086	2.753
Germany	0-12	3.243	2.349	1.733	2.088	1.497	1.093	1.735	1.200	0.842
	0-30	7.557	3.939	2.326	5.703	2.805	1.572	5.978	2.654	1.345
Italy	0-12	4.836	3.678	2.842	4.081	3.050	2.313	1.731	1.304	1.003
	0-30	7.527	4.672	3.216	6.469	3.934	2.646	4.280	2.177	1.305
Japan	0-12	4.536	3.324	2.476	3.302	2.410	1.789	1.983	1.496	1.148
	0-30	7.674	4.544	2.955	5.913	3.419	2.182	3.431	2.041	1.351
UK	0-12	3.215	2.234	1.567	2.350	1.617	1.123	0.959	0.667	0.472
	0-30	7.008	3.667	2.109	5.924	2.973	1.635	3.032	1.430	0.748
US	0-12	5.944	4.179	2.971	5.036	3.548	2.528	1.161	0.893	0.697
	0-30	11.481	6.220	3.731	9.976	5.359	3.200	2.446	1.339	0.855

Notes:

a Foreign currency sales in year t converted to $US in year t using exchange rate in year t.

b $US in year t converted to constant $US 1992 using US GDP deflator.

c Global molecules are molecules available in all seven countries, local molecules are those not available in the US.

For global and US-matched molecules, the per capita revenue over the first 12 years is lower in all countries than in the US, regardless of the discount rate or exchange rate basis. However, the magnitudes of the differentials and the rankings of some countries are quite different for life cycle revenues than for point-in-time price levels, which is the usual basis of comparison. For purposes of comparison, Table 5 shows

Table 3b **Mean Life Cycle Revenues Per Molecule for Global, US-Matched and Local Molecules**
Discounted Present Values, $1992 US[b], Converted to $US at Sales Date Exchange Rates[a]

Relative to the US (US=1)										
		Global Molecules[c] Discount Rate			US-Matched Molecules Discount Rate			Local Molecules[c] Discount Rate		
Country	**Age**	**0%**	**5%**	**10%**	**0%**	**5%**	**10%**	**0%**	**5%**	**10%**
Canada	0-12	0.953	0.956	0.957	0.940	0.949	0.956	2.009	1.988	1.960
	0-30	0.820	0.876	0.912	0.813	0.870	0.911	1.123	1.477	1.710
France	0-12	0.858	0.907	0.966	0.842	0.879	0.923	2.959	2.747	2.557
	0-30	0.839	0.878	0.936	0.837	0.865	0.907	4.284	3.798	3.220
Germany	0-12	0.546	0.562	0.583	0.415	0.422	0.432	1.494	1.344	1.208
	0-30	0.658	0.633	0.623	0.572	0.523	0.491	2.444	1.982	1.573
Italy	0-12	0.814	0.880	0.957	0.810	0.860	0.915	1.491	1.460	1.439
	0-30	0.656	0.751	0.862	0.648	0.734	0.827	1.750	1.626	1.526
Japan	0-12	0.763	0.795	0.833	0.656	0.679	0.708	1.708	1.675	1.647
	0-30	0.668	0.731	0.792	0.593	0.638	0.682	1.403	1.524	1.580
UK	0-12	0.541	0.535	0.527	0.467	0.456	0.444	0.826	0.747	0.677
	0-30	0.610	0.590	0.565	0.594	0.555	0.511	1.240	1.068	0.875
US	0-12	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0-30	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Notes:

a Foreign currency sales in year t converted to $US in year t using exchange rate in year t.

b $US in year t converted to constant $US 1992 using US GDP deflator.

c Global molecules are molecules available in all seven countries, local molecules are those not available in the US.

the 1992 point-in-time price indexes for each country relative to the US, based on US-matching molecules.[17]

17 The unit of analysis for the indexes in Table 5 is the molecule/therapeutic category (MOL/ATC). Thus these indexes include all molecules that match between the foreign country and the US and are in a common therapeutic category. The great majority of molecules are in only one ATC.

Table 4a **Mean Life Cycle Revenues Per Molecule for Global, US-Matched and Local Molecules**
Discounted Present Values, $1992 US[b], Converted to $US at Launch Date Exchange Rates[a]

US $ Per 1,000 Population										
		Global Molecules[c] Discount Rate			US-Matched Molecules Discount Rate			Local Molecules[c] Discount Rate		
Country	Age	0%	5%	10%	0%	5%	10%	0%	5%	10%
Canada	0-12	5.471	3.862	2.754	4.578	3.257	2.344	2.222	1.696	1.311
	0-30	9.791	5.529	3.394	8.464	4.749	2.915	2.649	1.905	1.410
France	0-12	4.947	3.680	2.794	4.115	3.024	2.268	3.371	2.390	1.730
	0-30	10.591	5.788	3.590	9.219	4.937	2.994	11.785	5.592	2.933
Germany	0-12	3.079	2.278	1.722	1.954	1.428	1.068	1.594	1.127	0.811
	0-30	5.962	3.416	2.173	4.313	2.342	1.423	4.121	2.049	1.151
Italy	0-12	4.702	3.593	2.798	3.903	2.929	2.238	1.703	1.289	0.994
	0-30	9.755	5.403	3.459	8.385	4.538	2.825	6.705	2.955	1.555
Japan	0-12	4.315	3.282	2.541	3.121	2.372	1.837	1.773	1.388	1.104
	0-30	6.170	4.039	2.852	4.665	2.998	2.091	2.512	1.681	1.219
UK	0-12	3.153	2.167	1.509	2.317	1.576	1.085	0.949	0.652	0.458
	0-30	8.222	4.039	2.201	7.068	3.339	1.738	3.705	1.661	0.819
US	0-12	5.944	4.179	2.971	5.036	3.548	2.528	1.161	0.893	0.697
	0-30	11.481	6.220	3.731	9.976	5.359	3.200	2.446	1.339	0.855

Notes:

a Foreign currency sales in year t converted to $US in year t using exchange rate at molecule launch date.

b $US in year t converted to constant $US 1992 using US GDP deflator.

c Global molecules are molecules available in all seven countries, local molecules are those not available in the US.

Comparing 1992 point-in-time prices (Table 5), France has the lowest price level relative to the US: 30-58 percent lower, depending on whether US-weighted (Laspeyres) indexes or French-weighted (Paasche) indexes are used. But comparing 12 or 30 year per capita revenues for US-matched molecules (Tables 3 and 4), France's level is

Table 4b **Mean Life Cycle Revenues Per Molecule for Global, US-Matched and Local Molecules**
Discounted Present Values, $1992 US[b], Converted to $US at Launch Date Exchange Rates[a]

Relative to the US (US=1)										
		Global Molecules[c] Discount Rate			US-Matched Molecules Discount Rate			Local Molecules[c] Discount Rate		
Country	**Age**	**0%**	**5%**	**10%**	**0%**	**5%**	**10%**	**0%**	**5%**	**10%**
Canada	0-12	0.920	0.924	0.927	0.909	0.918	0.927	1.914	1.899	1.880
	030	0.853	0.889	0.910	0.848	0.886	0.911	1.083	1.423	1.649
France	0-12	0.832	0.881	0.940	0.817	0.852	0.897	2.904	2.676	2.482
	0-30	0.922	0.931	0.962	0.924	0.921	0.936	4.818	4.176	3.430
Germany	0-12	0.518	0.545	0.580	0.388	0.402	0.422	1.373	1.262	1.164
	0-30	0.519	0.549	0.582	0.432	0.437	0.445	1.685	1.530	1.346
Italy	0-12	0.791	0.860	0.942	0.775	0.826	0.885	1.467	1.443	1.426
	0-30	0.850	0.869	0.927	0.841	0.847	0.883	2.741	2.207	1.819
Japan	0-12	0.726	0.785	0.855	0.620	0.669	0.727	1.527	1.554	1.584
	0-30	0.537	0.649	0.764	0.468	0.559	0.653	1.027	1.255	1.426
UK	0-12	0.530	0.519	0.508	0.460	0.444	0.429	0.817	0.730	0.657
	0-30	0.716	0.649	0.590	0.709	0.623	0.543	1.515	1.240	0.958
US	0-12	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	0-30	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Notes:

a Foreign currency sales in year t converted to $US in year t using exchange rate at molecule launch date.

b $US in year t converted to constant $US 1992 using US GDP deflator.

c Global molecules are molecules available in all seven countries, local molecules are those not available in the US.

only 6-18 percent lower than the US, depending on the discount rate and exchange rate used. Conversely, whereas Germany's price level exceeds that of the US for the Laspeyres index in Table 5 (US weights), Germany has the lowest discounted per capita revenues for US-matched molecules (Tables 3 and 4): just 39-43 percent of US levels for the first 12 years, and 43-57 percent of US per capita revenues for

Table 5 **Price Indexes Relative to the US, 1992**
All Single-molecule Drugs, Matched by MOL/ATC, Outpatient Pharmacy Sales

Country	Laspeyres-PSU	Paasche-PKG	N
Canada	1.030	0.664	458
France	0.701	0.416	412
Germany	1.273	0.521	471
Italy	0.907	0.331	406
Japan	0.923	0.486	396
UK	0.761	0.479	453
US	1.000	1.000	922

Notes:
Laspeyres = US weights.
Paasche = foreign weights.
PSU = price per standard unit.
PKG = price per gram.
MOL/ATC = molecule/therapeutic category.

the full 30 years, with the increase reflecting the higher per capita consumption of older molecules in Germany.

The UK has the lowest per capita expenditures of all countries for global molecules, regardless of the discount rate, for both 12 and 30-year life cycles, using sales date exchange rates. Using launch date exchange rates, the UK is either lowest or second lowest after Germany for the first 12 years, depending on the discount rate used. Over the full 30-year life cycle, German average per capita revenues per molecule, based on launch date exchange rates, are the lowest.

In Canada, France, Italy and Japan, per capita revenues per molecule relative to the US are generally lower for the full 30-year life cycle than for the first 12 years, indicating that the value of sales in these countries declines relative to US sales after patent expiration. The two exceptions are Germany and the UK, for which the 30-year sales ratios are higher than the 12-year sales. For the UK, this reflects the relatively high volume of older molecules (see Figures 2a and 2b). As discussed earlier, for other countries the decline in per capita sales rela-

tive to the US after patent expiration reflects the more rapid decline in those countries' prices, which more than offsets the generally higher volumes per capita of older drugs. These 30-year differences are less at launch date exchange rates than at year of sale exchange rates. As with prices, these measures of excess US life cycle sales, relative to non-US sales, are exaggerated because the US sales data do not reflect discounts to managed care and public buyers. Moreover, to the extent that generic shares are relatively large in the US, these differences in total revenues overstate US revenues that accrue to originator firms.

Not surprisingly, the 30-year measures of relative life cycle revenues are more sensitive to the discount rate than the 12-year measures. In particular, using a higher discount rate generally increases foreign revenues relative to the US, because the relatively high US sales at later ages receive less weight at higher discount rates. For example, for Italy, 30-year per capita revenues per molecule for global molecules are 65.6 percent of US levels with no discounting and using sales date exchange rates but are 86.2 percent of US levels using a 10 percent discount rate (Table 3).

The 12-year revenues per molecule for global molecules show Canada, France and Italy with less than 7 percent lower life cycle per capita revenues than the US, at either sales or launch date exchange rates, using the 10 percent discount rate as the most reasonable estimate of the real cost of capital for pharmaceutical firms. Japan would probably be at a similar level to these four countries or even higher, after reasonable adjustment for the downward bias in our data on outpatient sales in Japan. By contrast, Germany and the UK are over 40 percent lower than the US. Thus the conventional view of the UK and Germany as relatively high price countries is misleading as a guide to life cycle per capita revenues.

3.7 Number of Competitors

Figure 5 shows the mean number of manufacturers per molecule over the life cycle. The existence of multiple manufacturers at ages before patent expiration presumably reflects licensed co-marketing and co-

promotion arrangements. The increase in number of manufacturers after patent expiration reflects the entry of generic competitors. Thus although our data do not identify originator, licensee and generic producers, these data on number of manufacturers provide some evidence of cross-national differences in number of generic competitors and hence of the potential for upward bias in our estimates of life cycle revenues that accrue to originators at post-patent ages.

Italy has the largest number of manufacturers per molecule through to age seven, which is consistent with anecdotal reports that the regulatory system in Italy (and possibly France and Japan) has encouraged co-marketing with local manufacturers in return for higher regulated prices. Japan has a relatively large number of manufacturers throughout the life cycle, particularly at older ages although fewer than in Germany and the US. This relatively large number of manufacturers for older molecules in Japan, despite a very small generic market, may reflect pressures for co-promotion with local manufacturers that existed for older molecules but has declined for more recent molecules.

These data on numbers of competitors suggest that our molecule estimates of life cycle revenues for the 30-year life are most likely to be upward biased estimates of originator revenues for the US, followed by Germany. After age eight, the US has more manufacturers per molecule than any other country, and this excess grows rapidly in the early years after patent expiration and then again after age 20. Although the larger size of the US market is expected to support more manufacturers, the fact that the US has fewer molecules than several much smaller countries suggests that the US's larger number of generic manufacturers per molecule reflects competitive incentives, not simply market size.[18] Germany, which also has a very robust generic market, also shows a sharp increase in number of competitors after patent expiration, but this generic entry occurs about three years later

18 For evidence on the effect of number of competitors on price competition, see Danzon and Chao (2000b,c)

in the life cycle in Germany than in the US. The UK and Canada have few manufacturers per molecule, despite significant generic shares of prescriptions, which reflects the greater concentration of the generic drug industry in the UK and Canada than in the US or Germany. For the UK, our estimates of number of manufacturers understate the extent of competitive pressure on prices because we are unable to distinguish between parallel imports and UK-based originator products.

4 LIMITATIONS OF THE ANALYSIS

The estimates of cross-national differences in discounted present value of life cycle expenditure per capita, for global or US-matched molecules, provide the best available measures of the relative contributions of different countries to the common costs of R&D on a per capita basis. However, these estimates are subject to several limitations, reflecting the constraints of the data.

First, the measures here are based on gross revenues, whereas measures of manufacturer net revenues or contributions to joint costs should subtract out country-specific costs but such data are not available. However, this apparent limitation is less serious than it might seem, because of the arbitrariness of accounting allocations of joint costs. Joint costs include R&D, which is a global joint cost, and primary production of the active ingredient, which is typically concentrated in one or two sites per company worldwide to take advantage of scale economies. Secondary production (processing and packaging) facilities often serve multiple countries, and even promotion and marketing expenditures may be country-specific but joint across several products. Accounting allocation of these joint costs through transfer pricing is driven largely by tax and regulatory concerns, whereas economic considerations would allocate joint costs based on demand. Thus, even if country-specific accounting data on costs were available, such data would at best be a rough approximation to true economic costs.[19] Country-specific costs related to promotion, secondary production and sales may differ due to market and regulatory conditions in each country. To the extent that higher gross sales are associated with higher variable costs of production and promotion, our cross-national differences in gross revenues overstate differences in net revenues. This is most likely for countries such as France, where relatively

19 Grabowski and Vernon (1990) report rough estimates for the US of variable costs as a percent of sales, and use estimates of average cost per new chemical entity to calculate the net return or profit of R&D. These calculations estimate non-US net sales simply by applying a multiplier of roughly two to US revenues. Neither this nor other previous studies decompose life cycle revenues into prices and volumes, either for the US or for other countries.

high per capita gross revenue reflects high volume rather than high prices,.

Second, the market and regulatory environment has changed in most countries since the period of our data. In the US, per capita volumes have increased, with the growth of outpatient drug coverage in the 1990s, while post-launch price growth has moderated. Other countries have experienced changes in their regulatory regimes. Because all countries have changed, the effect on relative net revenues across countries is unpredictable.

Third, our estimates are for total revenue for the molecule, which overstates the returns to originator firms to the extent that revenues accrue to licensees and generics. The potential bias from including licensee revenues is probably small, assuming that on average a licensee assumes costs that roughly offset their share of revenues. Including generic revenues is a more significant source of upward bias, because generics in some countries capture a dominant share of post-patent revenues but incur none of the costs of R&D and promotion that are borne by originators. Generic market shares differ significantly across countries and have changed over time as a result of reimbursement and regulatory changes in several countries, notably the US and Germany.[20] Our measures of life cycle revenues are therefore upward biased as measures of revenues accruing to innovator firms for countries with significant generic market shares, notably the US, the UK, Canada and Germany. This bias should be small for the 12-year life cycle estimates, assuming a 10-12 year life with patent protection, on average. The upward bias could be significant for the 30-year life esti-

20 In the US, the 1984 Waxman-Hatch Drug Price Competition and Patent Term Restoration Act extended patent life for originator firms up to five years to offset time lost due to regulatory delay, but also reduced the costs and regulatory delay faced by generics. For early effects, see Grabowski and Vernon (1992). Generic market share in Germany grew following the adoption of reference pricing in 1989 and physician drug budgets in 1993. Accurate data on generic market shares are not readily available all countries. Ikegami et al. (1994) report generic market share of 11 percent in Japan.

mates for countries where generics capture most of the post-patent sales. However, the bias in discounted present value is smaller, the higher the discount rate used, because sales that accrue late in the molecule life are most affected by discounting.

Fourth, our estimates of prices and revenues in the UK and the US are further upward biased because our data do not reflect manufacturer discounts given to managed care and public purchasers in the US and discounts to pharmacists in the UK. Adjusting for generic shares and discounts might yield US per capita revenues that are comparable to those of other high expenditure countries such as France. Similar adjustments for the UK would lower its per capita revenue estimates further, relative to some other countries but not necessarily relative to the US and possibly Germany and Canada, which also have large generic shares.

Fifth, our estimates are based on molecules for which sales are observed at each age, without adjustment for the probability of market exit before age 30. The age-specific revenues should therefore be viewed as estimates conditional on the molecule remaining on the market. These conditional estimates of life cycle revenue may be upward biased for the unconditional expected revenue for the average molecule. In addition, because the synthetic life cycle profiles we have constructed reflect different drug cohorts at different ages, if these cohorts differ – for example, more recent drugs are intrinsically more valuable – then our estimates of age-price profiles could be biased. However, if such survivor and cohort biases exist, they apply to all countries, hence the cross-national comparisons are not necessarily biased.

Sixth, from the perspective of manufacturers' returns, the life cycle revenue estimates should ideally be adjusted for cross-country differences in average country-specific launch delay, because delay reduces discounted present values.[21] Unfortunately, the data available to us on

21 For estimates of cross-country differences in launch delays see, for example, Lasagna (1989), Wardell (1973, 1978), Schweitzer et al. (1996), Dranove and Melzer (1994). These studies show that delays in some countries have changed over time and differ by type of drug. Thus any attempt to adjust our estimates for launch delays could not simply use a constant delay for each country.

country-specific molecule launch dates are inadequate to estimate launch lags. However, to the extent that launch dates reflect the choices of manufacturers in addition to external regulatory constraints, even if launch lags were known the interpretation would be ambiguous.[22] Thus, as with costs, the lack of data on launch dates may not be as damaging as it might appear.

Finally, although the per capita gross revenue estimates are suggestive of contributions to common costs, no conclusions should be drawn about the appropriateness of different countries' contributions. These are gross measures, whereas net contributions also depend on costs. More importantly, there is no presumption that per capita contributions should be equal between countries. On the contrary, Ramsey pricing theory suggests that appropriate contributions depend on underlying preferences and true demand elasticities, which are unobservable. Rather, the purpose here is to demonstrate that comparisons based solely on prices at a single point in time in some cases provide very misleading estimates of each country's relative expenditures or gross contribution based on the full life cycle profiles of price and volume.

22 Dranove and Melzer (1994) report evidence suggesting that manufacturer strategies play an important role in determining launch lags in the US

5 CONCLUSIONS

This analysis has shown that the pattern of price, volume and sales revenue per capita over the life of a molecule is quite different in different countries. For the global molecules, which are the same molecules in all countries, the US appears to have the highest discounted life cycle revenue per capita. However, the US data are upward biased as a measure of revenue to originator firms, because they do not net out discounts to managed care and public purchasers or sales that accrue to generics after patent expiry. If these factors together bias the US figures upward by roughly 5-10 percent, then the US per capita life cycle revenues would be comparable to those in France, Italy and Canada, assuming a 10 percent discount rate.

The UK tends to have relatively high launch prices, along with Germany and the US, but after age five the UK real prices are in the lower half of the price distribution across countries. Volume per capita for new molecules is relatively low in the UK compared to other countries, whereas older molecules have relatively high volumes. This pattern of slow diffusion and conservative prescribing, combined with low prices for older molecules, results in the UK having lower total per capita lifetime expenditures per molecule for global molecules than any of the other countries in the sample, at 51-72 percent of US levels, depending on the exchange rate, the discount rate and the length of life used in the calculation. These expenditure estimates at the molecule level are upward biased as a measure of revenue to originator firms in the UK because they do not reflect manufacturer discounts to pharmacists or generic sales.

By contrast, France has relatively low launch prices and persistent price decline over the life cycle. But because France has relatively high volume per capita throughout the life cycle, total lifetime expenditure per capita in France is second highest, at 83-97 percent of US levels, depending on the discount rate and length of life. France also has the highest per capita expenditures on local molecules (molecules that are available in the comparison country but not in the US), at 2.5-4.8 times the US level, depending on the exchange rate, the discount rate and length of molecule life cycle considered. The molecule estimates

for France are not upward biased by unobserved discounts or generic shares. If we could adjust for these sources of upward bias in other countries, notably the US, this would be likely to leave France with the highest per capita gross revenue to originator firms. However, France would probably rank lower on net revenue, assuming that the relatively high volume is associated with relatively high variable costs.

For Germany, the findings are reasonably consistent with conventional wisdom for prices but not for volumes or life cycle revenue. Germany has relatively high price per unit, compared to other countries, although the differential narrows at older molecule ages and is less for price per gram. But Germany has relatively slow diffusion of new molecules and relatively high utilization of older molecules, such that overall expenditure per capita for global molecules is second lowest of the countries studied, at 52-66 percent of the US level. Germany has relatively high expenditure per local molecule for the 30-year life and a large number of local molecules. Overall, Germany's high aggregate spending per capita appears to result more from its large number of molecules than from high expenditure per molecule.

For local molecules, per capita expenditures are higher in all countries than in the US, with the exception of the UK, which has lower per capita sales on local molecules than the US for the 12-year life, whatever the discount rate used, and for the 30-year life too if a 10 percent discount rate is used.

Japan has higher per capita sales than the US for local molecules, whereas the reverse is true for global molecules. Since our data are downward biased for total outpatient sales in Japan, Japan's true gross sales for global molecules are probably close to US levels and for local molecules the excess is even greater than reported here.

These findings confirm that, compared to the other countries in our sample, the UK and the US tend to spend less absolutely on local molecules that have not achieved broad diffusion, which plausibly are less effective molecules. Other countries spend more absolutely and devote a larger fraction of their total drug spending to these less broadly diffused, local molecules.

For the global molecules, the lifetime revenue per capita measures provide the best available measure of the contribution of different countries to the common costs of R&D, because they combine price and volume over a molecule's entire life cycle. However, as measures of relative contributions they are imperfect for several reasons. First, these gross sales measures overstate net revenues, i.e. gross revenues less the variable costs of production and sales. This upward bias is greater in countries with high volume but low prices, such as France. Second, these measures of gross per capita revenue include sales of generics as well as originator products. These estimates therefore provide a more upward biased measure of returns to originator R&D for the 30-year life than the 12-year life, particularly for countries where generics capture a large market share after patent expiration, such as the US, Germany, the UK and Canada. Third, these gross sales figures do not reflect discounts to pharmacists in the UK and rebates to managed care and public payers in the US.

Taking these various sources of bias roughly into account, using 10 percent discount rates and sales date exchange rates the UK has lower per capita lifetime expenditures per molecule than other countries. For the other countries, these lifetime expenditure comparisons overturn at least some of the conventional conclusions based on point-in-time price comparisons. In particular, France and Italy are closer to the US than appears from simple price comparisons, with less than 9 percent lower per capita revenues for the 12-year life. Germany had average prices comparable to the US in 1992, but is second lowest (after the UK) in terms of life cycle revenue per capita for both global and US-matched molecules, although not for local molecules.

Since this is a descriptive study, it does not provide a basis for detailed policy conclusions. However, the results do indicate the limitations of single point-in-time price comparisons as a measure of the relative contributions of different countries to the common costs of R&D. If international comparisons are to be used as a basis for price regulation, then the comparison should take into account cross-national differences in the full life cycle path of prices and volumes, not simply prices at launch or at any other single point in time.

REFERENCES

Baumol, W.J. and D.F. Bradford, 1970. 'Optimal Departures from Marginal Cost Pricing.' *American Economic Review.* 265-83.

Berndt, E., Z. Griliches and J. Rosett, 1993. 'Auditing the Producer Price Index – Microevidence from Prescription Pharmaceutical Preparations.' *Journal of Business and Economic Statistics.* 11 (3): 251-64.

Bureau European des Unions de Consommateurs (BEUC), 1989. *Drug Prices and Drug Legislation in Europe.* Brussels.

Burstall, M.L., 1991. 'Europe after 1992: Implications for Pharmaceuticals.' *Health Affairs.* 9:157-171.

Caves, R. E., M.D. Whinston and M.A. Hurwitz, 1991. 'Patent Expiration, Entry, and Competition in the US Pharmaceutical Industry.' *Brookings Papers on Economic Activity: Microeconomics.* 1-66.

Danzon, P.M., 1996. 'Defined Daily Doses for Pharmaceuticals: Risks and Potential.' Working Paper. Philadelphia: Health Care Systems Department, The Wharton School.

Danzon, P.M., 1997a. *Trade and Price Differentials for Pharmaceuticals: Policy Options.* London: Office of Health Economics.

Danzon, P.M., 1997b. 'Price Discrimination for Pharmaceuticals: Welfare Effects in the US and the EU.' *International Journal of the Economics of Business.* 4(3): 301-321.

Danzon, P.M. and L.W. Chao, 2000a. 'Cross-National Price Differences for Pharmaceuticals: How Large and Why?' *Journal of Health Economics.* 19: 159-195.

Danzon, P.M. and L.W. Chao, 2000b. 'Does Regulation Drive out Competition in Pharmaceutical Markets?' *Journal of Law and Economics.* 43(2): 311-357.

Danzon, P.M. and L.W. Chao, 2000c. *Prices, Competition and Regulation in Pharmaceuticals: a Cross-National Comparison.* London: Office of Health Economics.

Danzon, P.M. and J.D. Kim, 1998. 'International Price Comparisons for Pharmaceuticals: Measurement and Policy Issues.' *PharmacoEconomics.* 14(1): 115-128.

DiMasi, J. et al., 1991. 'The Cost of Innovation in the Pharmaceutical Industry.' *Journal of Health Economics.* 10:107-142.

Dranove, D. and D. Melzer, 1994. 'Do Important Drugs Reach the Market Sooner?' *Rand Journal of Economics.* 25(3): 402-23.

Grabowski, H.G. and J.M. Vernon, 1990. 'A New Look at the Returns and Risks to Pharmaceutical R&D.' *Management Science.* 36(7): 804-21.

Grabowski, H.G. and J.M. Vernon, 1992. 'Brand Loyalty, Entry and Price Competition in Pharmaceuticals after the 1984 Act.' *Journal of Law and Economics.* 35(2): 331-50.

Grabowski, H.G. and J.M. Vernon, 1996. 'Prospects for Returns to Pharmaceutical R&D under Health Care Reform.' In *Competitive Strategies in the Pharmaceutical Industry,* ed. R.B. Helms. Washington, DC: American Enterprise Institute Press: 194-207.

Ikegami, N., W. Mitchell and J. Penner-Hahn, 1994. 'Pharmaceutical Prices, Quantities and Innovation: Comparing Japan with the US.' *PharmacoEconomics.* 6(5): 424-33.

Lasagna, L., 1989. 'Congress, the FDA, and the New Drug Development: Before and After 1962.' *Perspectives in Biology and Medicine.* 32(2).

Lu, J.C. and W.S. Comanor, 1994. *Strategic Pricing of New Pharmaceuticals.* Los Angeles: School of Public Health, University of California at Los Angeles.

Myers, S.C. and L. Shyam-Sunder, 1996. 'Measuring Pharmaceutical Industry Risk and the Cost of Capital.' In *Competitive Strategies in the Pharmaceutical Industry,* ed. R.B. Helms. Washington, DC: The American Enterprise Institute Press: 208-237.

Ramsey, F.P., 1927. 'A Contribution to the Theory of Taxation.' *Economic Journal.* 37: 47-61.

Reekie, W., 1978. 'Price and Quality Competition in the United States Drug Industry.' *Journal of Industrial Economics.* 26(3): 223-37.

Schweitzer, S.O., M.E. Schweitzer and M.S. Guellec, 1996. 'Is There a US Drug Lag? The Timing of New Pharmaceutical Approvals in the G-7 Countries and Switzerland.' *Medical Care Research and Review.* 53(2): 162-178.

US Congress, Office of Technology Assessment (OTA), 1993. *Pharmaceutical R&D: Costs, Risks and Rewards.* Washington DC: Government Printing Office.

US General Accounting Office (GAO), 1992. *Prescription Drugs: Companies Typically Charge More in the United States Than in Canada.* Washington, DC: Government Printing Office.

US General Accounting Office (GAO), 1994. *Prescription Drugs: Companies Typically Charge More in the United States than in the UK.* Washington, DC: Government Printing Office.

US House of Representatives, Committee on Government Reform and Oversight, Minority Staff Report, Prepared for Rep. Thomas A. Allen, 1998. *Prescription Drug Pricing in the 1st Congressional District in Maine: an International Price Comparison.* October 24, 1998.

Wardell, W., 1973. 'Introduction of New Therapeutic Drugs in the United States and Great Britain: an International Comparison.' *Clinical Pharmacology Therapeutics.* 14: 773-790.

Wardell, W., 1978. 'The Drug Lag Revisited: Comparisons by Therapeutic Area of Patterns of Drugs Marketed in the US and Great Britain from 1972 through 1976.' *Clinical Pharmacology and Therapeutics.* 24.

APPENDIX: ALGEBRAIC FORMULATIONS

Exchange Rate Adjustment Using Launch Date Exchange Rates

If LC_{ijt} denotes sales of molecule i in local currency of country j in year t, this is converted to constant 1992 $US as follows:

$$\$1992_{ijt} = LC_{ijt} \times (USD_{ij1}/LC_{ij1}) \times GDP^{us}_{t,92}$$

where USD_{ij1}/LC_{ij1} is the exchange rate between local currency j and the US dollar in the year of launch of molecule i in country j, and $GDP^{us}_{t,92}$ is the change in the US GDP deflator between year t and 1992.

Age-Specific Expenditure, Price and Volume per Capita

All reported sales data are converted to constant 1992 US dollars, using either sales date or launch date exchange rates and US GDP deflator inflation adjustment. For each country and molecule age, we compute country-specific expenditures per capita using reported sales for all molecules in the sample at that age in that country for any year in our observation period 1981-1992.

For example, for age s in country j, mean expenditure per capita e_{sj} is defined as:

$$e_{sj} = (1/n_{sjt}) \sum_{i=1}^{n_{sjt}} \sum_{t=t_1}^{T} E_{isj}^{t}/Z_j^{t}$$

where Z_j^t = population in country j in year t, t_1 = 1981, T = 1992, E_{isj}^t = total sales of molecule i in country j at age s in year t, and n_{sjt} = number of molecules in country j with sales at age s in year t.

Similarly, volume per capita for age s in country j, q_{sj}, is the average over all molecules at age s in country j:

$$q_{sj} = (1/n_{sjt}) \sum_{i=1}^{n_{sjt}} \sum_{t=t_1}^{T} Q_{isj}{}^{t}/Z_j{}^{t}$$

where $Q_{isj}{}^{t}$ is total units (either standard units or grams) sold for all products in molecule i at age s in year t in country j.

The unweighted mean price per unit at age s in country j is the average over all molecules of the molecule-specific average price per unit (averaged over products, presentations and strengths):

$$P_{sj} = (1/n_{sjt}) \sum_{i=1}^{n_{sjt}} E_{isj}{}^{t}/Q_{isj}{}^{t}$$

where $E_{isj}{}^{t}$ and $Q_{isj}{}^{t}$ are, respectively, total expenditure and total units (either standard units or grams) sold for molecule i at age s in year t in country j.

We also defined a weighted mean price per unit, which weights each molecule-age by its share of expenditures at that age:

$$P_{sj}{}^{w} = \sum_{i=1}^{n_{sj}} (E_{isj}{}^{t}/Q_{isj}{}^{t})\, w_{isj}$$

where w_{isj} is the share of total expenditures on molecules of age s in country j that is attributable to molecule i.

The discounted present value of lifetime revenue per capita for the average molecule in country j, PVR_j, is:

$$PVR_j = \sum_{s=1}^{S} e_{sj}\, (1+r)^{-s}$$

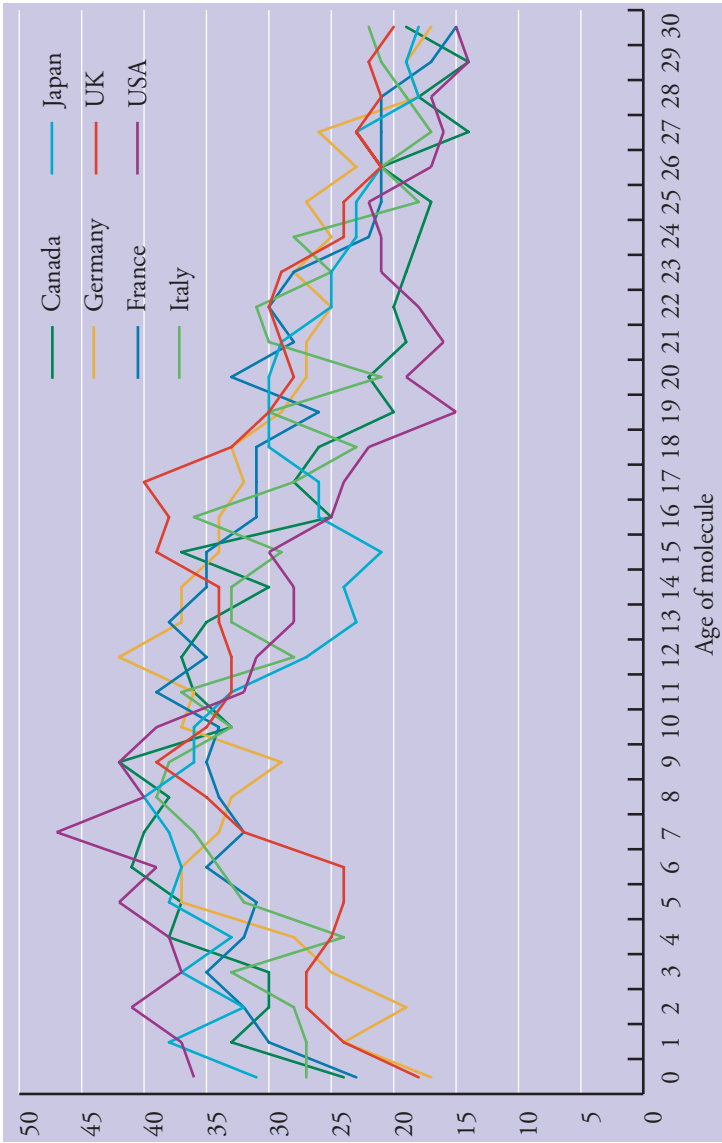
where r is the real discount rate and S is the number of years in the molecule's economic life.

We report results for values of r = 0, 5 and 10 percent. A discount rate of zero simply shows total life cycle revenue without discounting,

a 10 percent discount rate corresponds roughly to previous estimates of the real cost of capital for pharmaceutical firms,[23] and 5 percent is often used as a social discount rate.

23 DiMasi et al. (1991) estimate a beta of one for the pharmaceutical industry and a real cost of capital of 10 percent. Myers and Shyam-Sunder (1996) estimate a higher cost of capital for early stage research. Drawing on these ideas, US Congress OTA (1993) used a real average cost of capital of 11 percent.

Figure 1 **Number of Global Molecules, by Molecule Age[a]**



a Global molecules are molecules with sales in at least one year in each of the seven countries.

Figure 2a **Mean Volume (Standard Units) per 1,000 Population for Global Molecules, by Molecule Age**

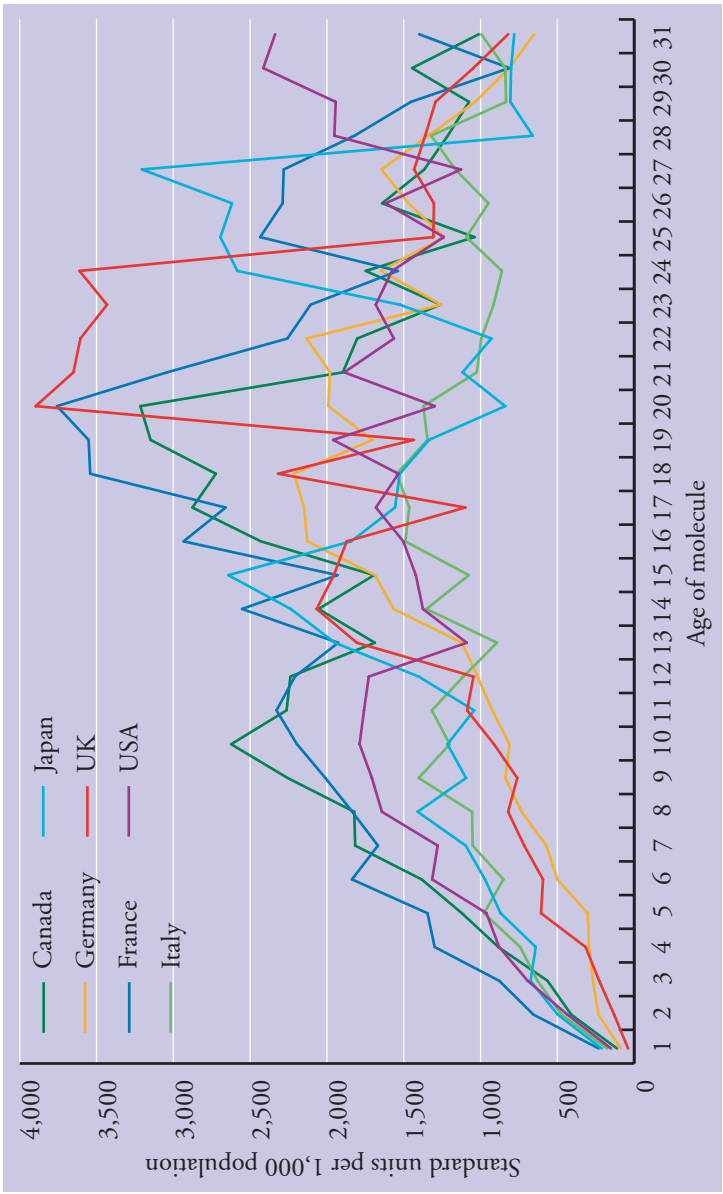


Figure 2b **Median Volume (Standard Units) per 1,000 Population for Global Molecules, by Molecule Age**

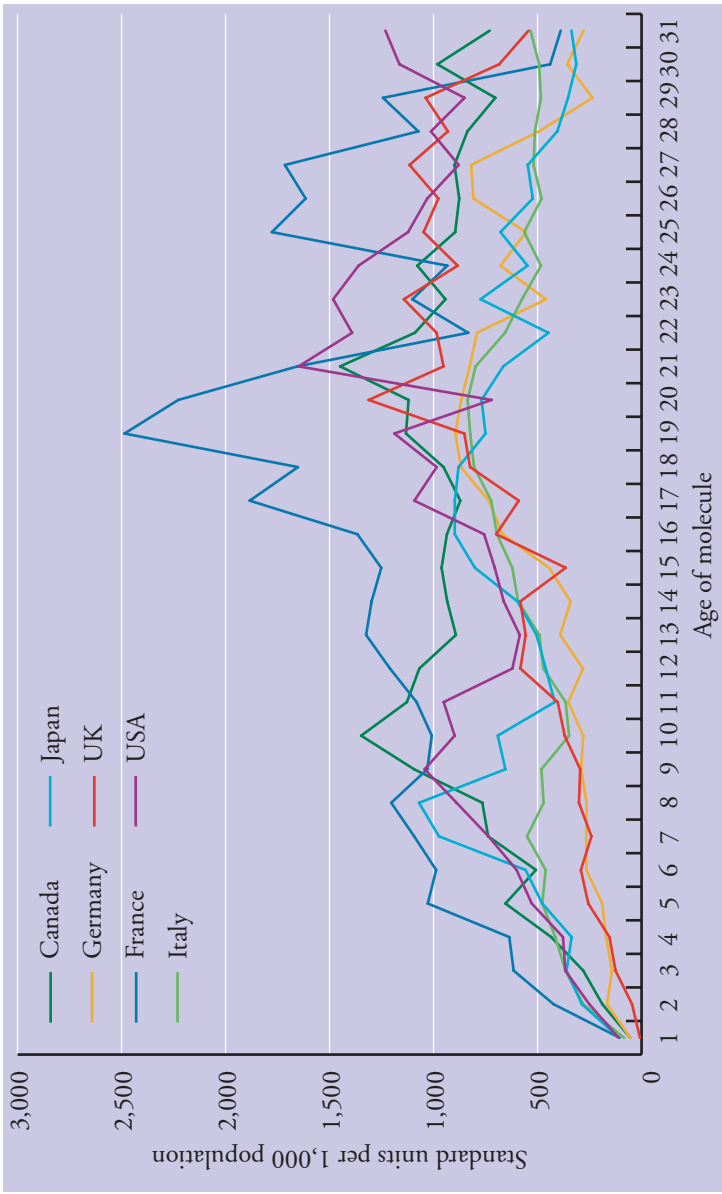


Figure 3a **Mean Revenue per 1,000 Population for Global Molecules, by Molecule Age, Sales Date Exchange Rates**

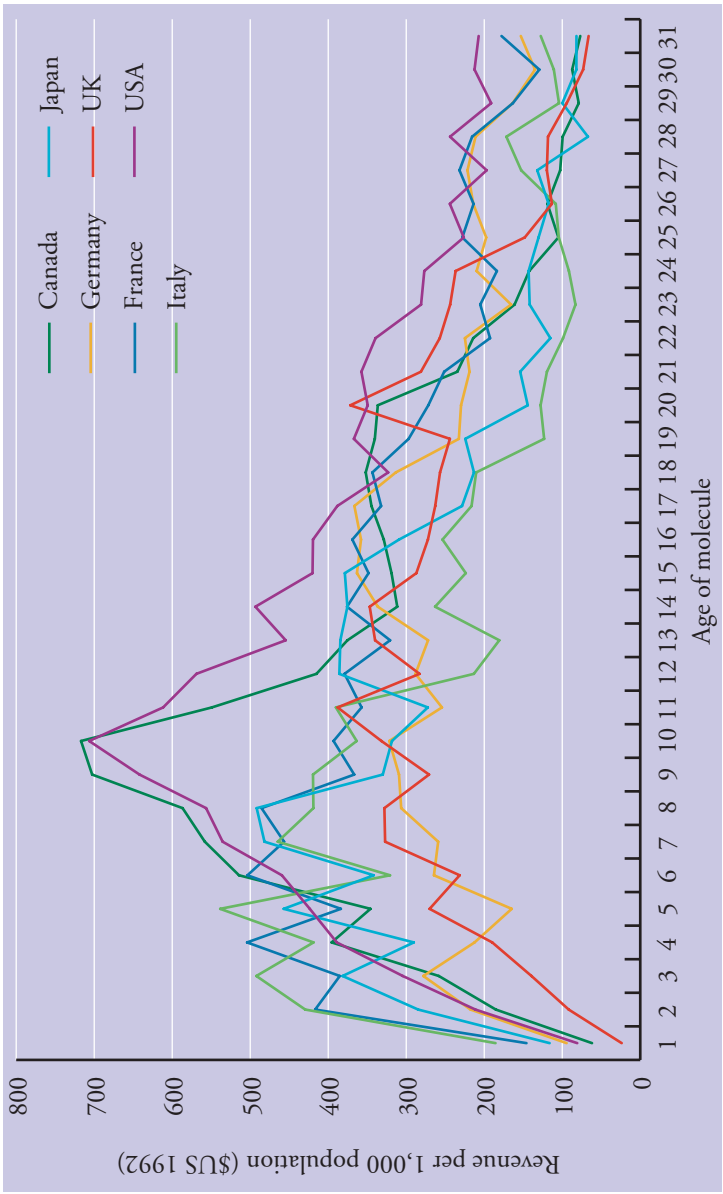


Figure 3b **Median Revenue per 1,000 Population for Global Molecules, by Molecule Age, Sales Date Exchange Rates**

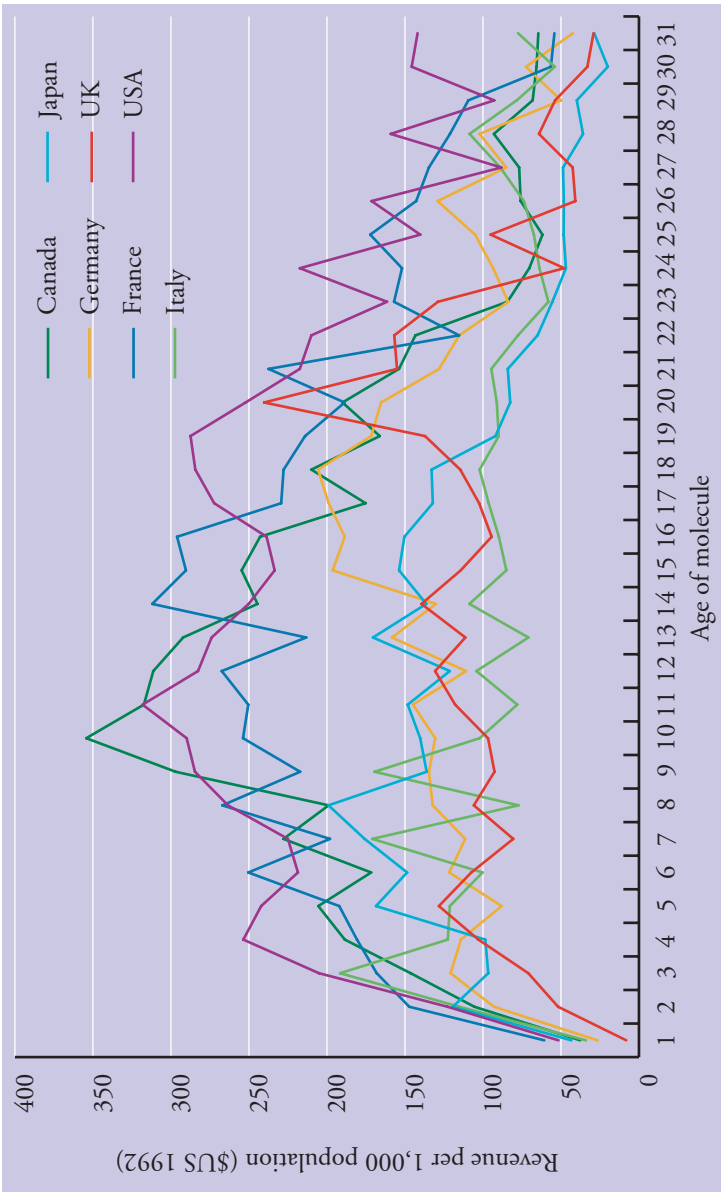


Figure 3c **Median Revenue per 1,000 Population for Global Molecules, by Molecule Age, Launch Date Exchange Rates**

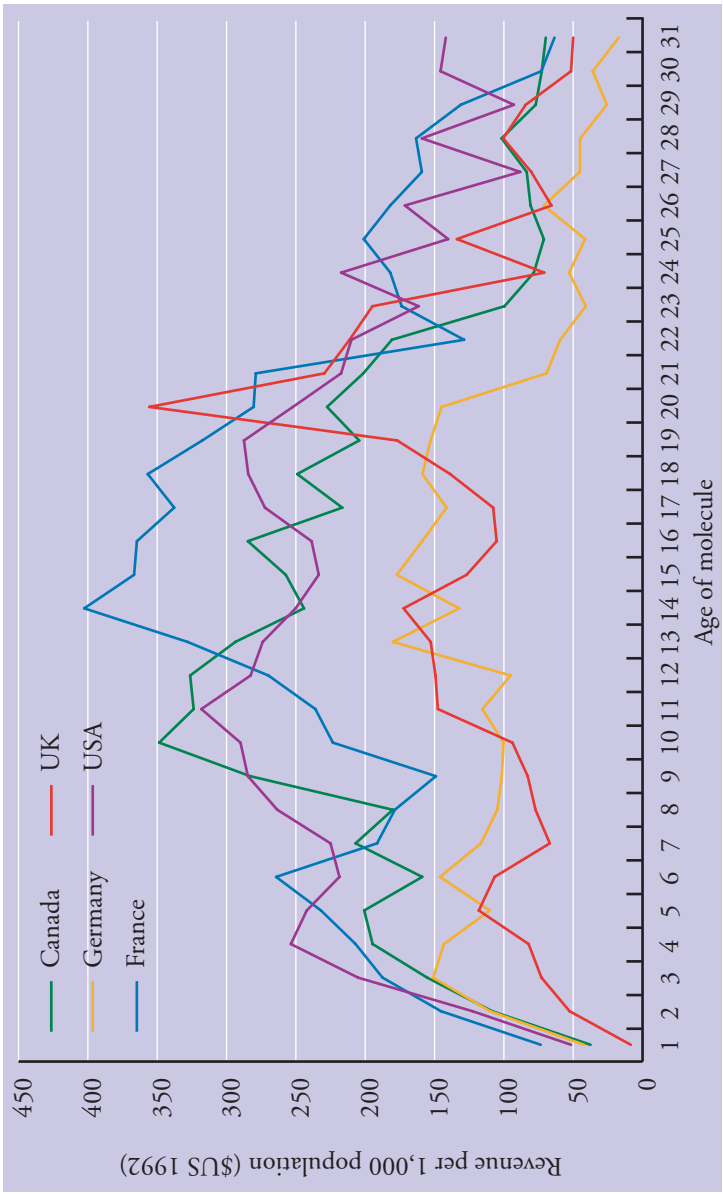


Figure 4a **Mean Price per Standard Unit, Unweighted, for Global Molecules, by Molecule Age, Sales Date Exchange Rates**

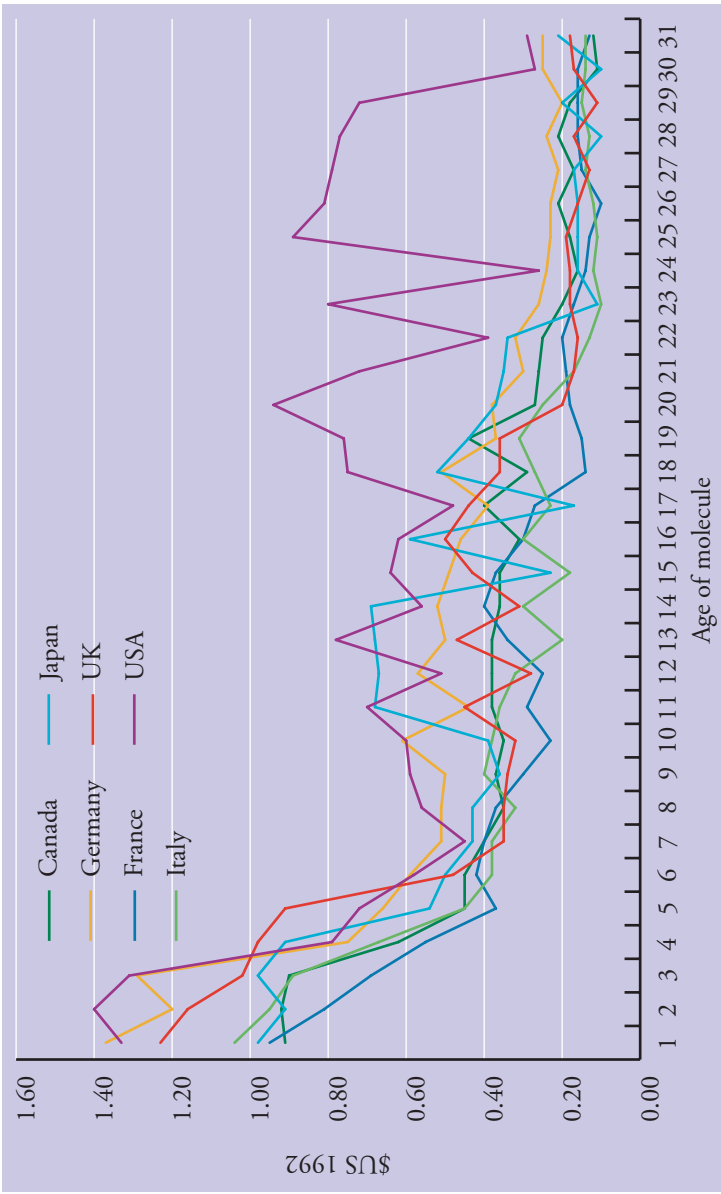


Figure 4b **Median Price per Standard Unit for Global Molecules, by Molecule Age, Sales Date Exchange Rates**

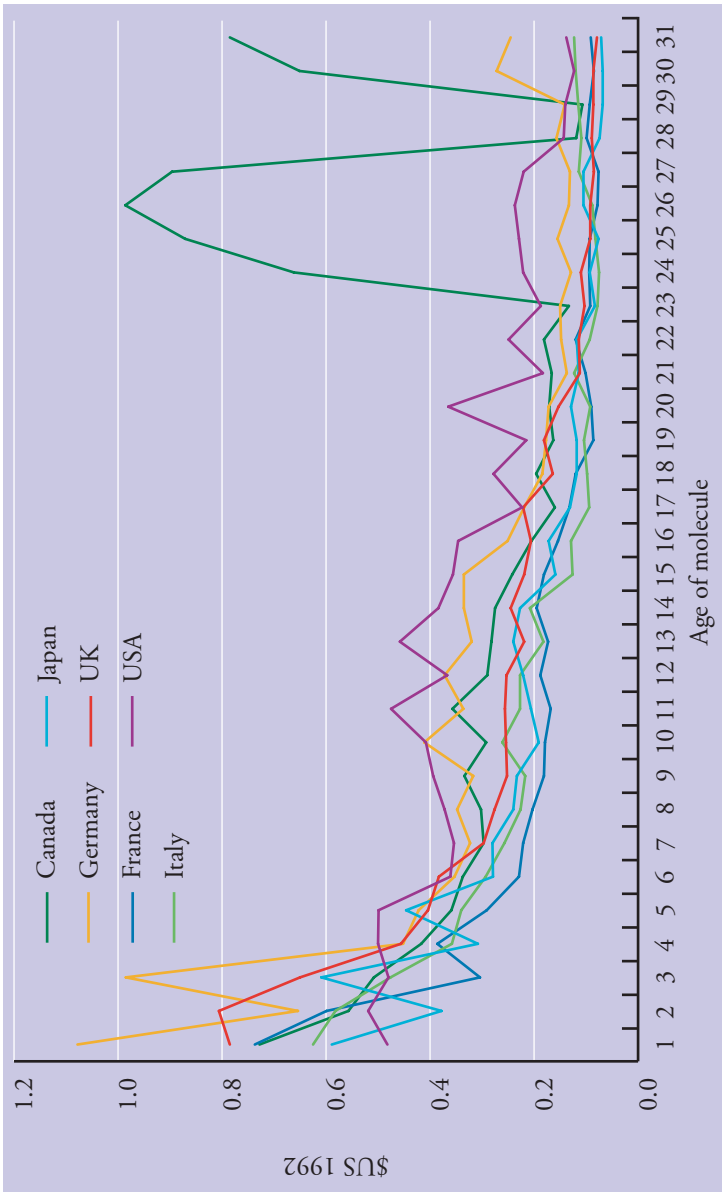


Figure 4c **Median Price per Gram for Global Molecules, by Molecule Age, Sales Date Exchange Rates**

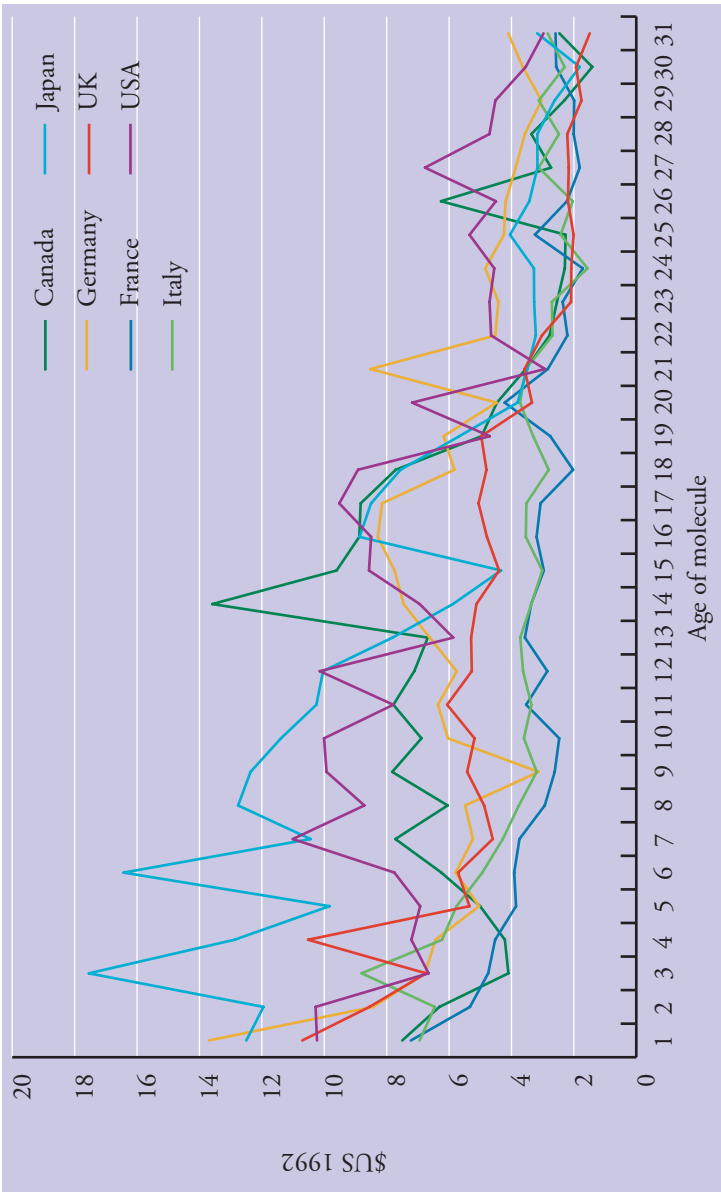
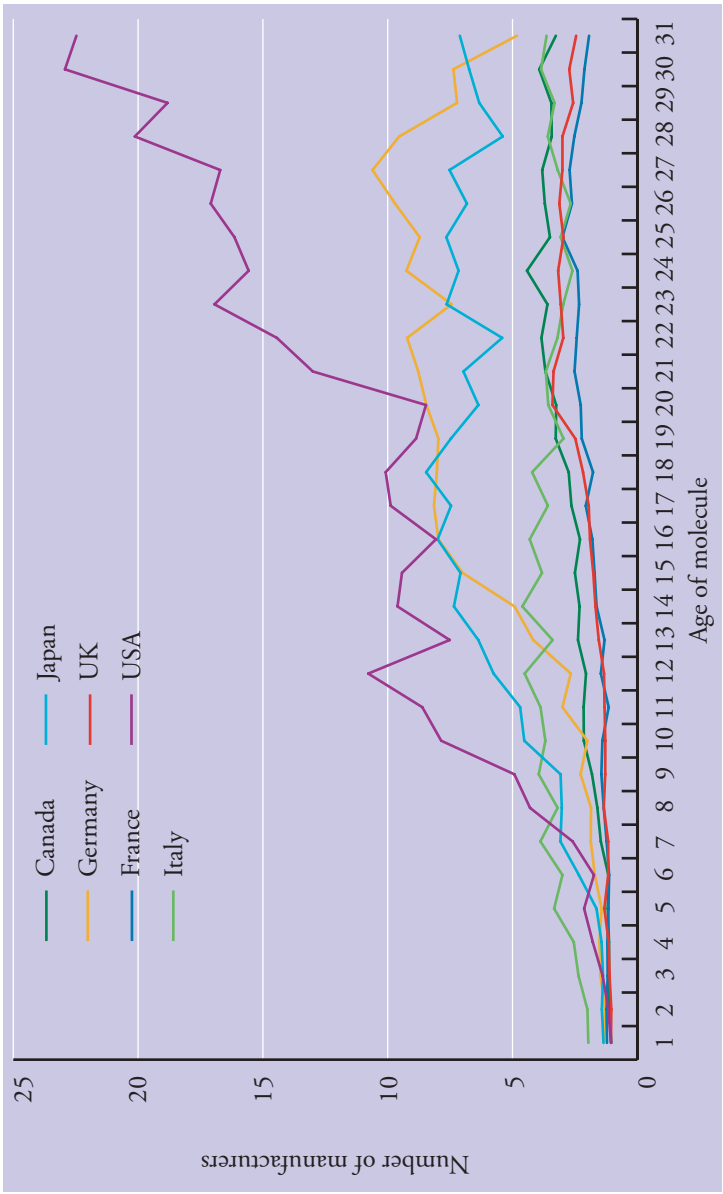


Figure 5 **Mean Number of Manufacturers per Molecule for Global Molecules, by Molecule Age**



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