IMPORTATION AND INNOVATION

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Importation of drugs into the US may soon become legal. Since prices of drugs are lower in most other countries than they are in the US, importation would result in a decline in US drug prices. The purpose of this paper is to assess the consequences of importation for new drug development.

First, the author presents a simple theoretical model of drug development which suggests that the elasticity of innovation with respect to the expected price of drugs should be at least as great as the elasticity of innovation with respect to expected market size (disease incidence). Then, the cross-sectional relationship between pharmaceutical innovation and market size among a set of diseases (different types of cancer) exhibiting substantial exogenous variation in expected market size is examined. Two different measures of pharmaceutical innovation are analysed: the number of distinct chemotherapy regimens for treating a cancer site and the number of articles published in scientific journals pertaining to drug therapy for that cancer site.

Both analyses indicate that the amount of pharmaceutical innovation increases with disease incidence. The elasticity of the number of chemotherapy regimens with respect to the number of cases is 0.53. The elasticity of MEDLINE drug cites with respect to cancer incidence throughout the world is 0.60. In the long run, a 10% decline in drug prices would therefore be likely to cause at least a 5–6% decline in pharmaceutical innovation. Evidence suggests that pharmaceutical industry employment would also decline (by at least 3.5–4%) in response to an exogenous 10% decline in drug prices.

Keywords: Pharmaceuticals; Importation; Innovation; Cancer; Chemotherapy; Employment

1 INTRODUCTION

Importation of drugs into the US may soon become legal. Since prices of drugs are lower in most other countries than they are in the US, importation would result in a decline in US drug prices. The price decline would benefit US consumers in the short run. However, importation may have two other effects that could reduce the welfare of US consumers. First, importation could reduce the quality, or safety, of drugs purchased by Americans and increase the number of adverse drug events. Second, importation could reduce the number of new drugs developed in the future by reducing the expected profitability of new drug development. In previous papers (Lichtenberg, 2005a, b, c), I have shown that the introduction of new drugs has increased the longevity and ability to work and reduced the utilization of hospitals and nursing homes.
Therefore, while importation may yield an increase in static efficiency (lower drug prices), it may also result in reduced dynamic efficiency (fewer new drugs developed). Schumpeter (1947, p. 190, italics in original) suggested that, in general, consumer welfare depends more on dynamic efficiency than it does on static efficiency: ‘we shall call that system relatively more efficient which we see reason to expect would in the long run produce the larger stream of consumers’ goods per equal unit of time.’

The purpose of this paper is to assess the consequences of importation for new drug development. One way to do this is to estimate the elasticity of drug development with respect to the expected price of drugs.\(^1\) This approach requires substantial exogenous variation in expected drug prices, which may be hard to find. I will pursue an alternative approach: I will attempt to estimate the elasticity of drug development with respect to expected market size. In Section 2, I will present a simple theoretical model of drug development which suggests that the elasticity of investment with respect to the expected price of drugs should be at least as great as the elasticity of investment with respect to expected market size. In Section 3, I will examine the cross-sectional relationship between pharmaceutical innovation and market size among a set of diseases (different types of cancer) exhibiting substantial exogenous variation in expected market size. In Section 3, I will consider the implications of the estimates and compare them to estimates from previous studies.

2 A SIMPLE THEORETICAL MODEL OF DRUG DEVELOPMENT

Suppose that the cost function of the pharmaceutical firm is linear, that is, there is a fixed cost and the marginal cost is constant:

\[
C = C_F + mQ = C_F + C_V
\]

where

- \(C\) = total cost
- \(C_F\) = fixed cost
- \(m\) = marginal cost
- \(Q\) = quantity
- \(C_V\) = variable cost = \(mQ\).

The fixed cost \((C_F)\) is likely to be very large relative to marginal cost. In 2003, the Tufts Center for the Study of Drug Development reported that the fully capitalized cost to develop a new drug, including studies conducted after receiving regulatory approval, averages $897 million.\(^3\) In 2002, the average US price of a generic prescription, which may be close to marginal cost, was $30.

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1 Abbott and Vernon (2005) review the literature on the linkages between pharmaceutical price regulation, profits, cash flows, and investment in R&D.
2 Danzon et al. (2005) and Kyle (2005) examine the effect of prices, or price controls, on the probability and timing of launch of existing drugs in different countries. Danzon et al. (2005) present evidence that countries with lower prices or smaller market size experience longer delays in access to new drugs. Kyle (2005) found that companies delay launch into price-controlled markets, and are less likely to introduce their products in additional markets after entering a country with low prices.
Given this cost function, the firm’s profit function is

\[ \Pi = R - C \]
\[ = PQ - (C_F + C_V) \]
\[ = PQ - mQ - C_F \]
\[ = R - C_V - C_F \]
\[ = \Pi_V - C_F \]  
(2)

where

\[ \Pi = \text{profit} \]
\[ R = \text{revenue} = PQ \]
\[ P = \text{price} \]
\[ \Pi_V = \text{variable profit} = \text{revenue} - \text{variable cost} = (P - m)Q. \]

The firm will be willing to invest (incur the fixed cost \( C_F \)) if it expects ‘variable profit’ (revenue – variable cost) to exceed fixed cost. This theory of investment in innovation is quite consistent with Scherer’s (2001, p. 220) ‘virtuous rent-seeking model’ of pharmaceutical industry R&D, in which, ‘as profit opportunities expand, firms compete to exploit them by increasing R&D investments, and perhaps also promotional costs, until the increases in costs dissipate most, if not all, supranormal profit returns.’

Suppose we regard both fixed and marginal cost as given. Exogenous changes in price or quantity change variable profit, and therefore may affect whether or not the firm is willing to invest.

If the firm were an unregulated monopolist facing a linear inverse demand curve \( P = a - bQ \), the profit-maximizing price would be \( P^* = (a + m)/2 \), and the profit-maximizing quantity would be \( Q^* = (a - m)/2b. \) However, suppose that the firm is prevented, by reimportation or regulation, from charging the profit-maximizing price. The actual price it can charge, \( P \), may be lower than \( P^* \). I want to assess the sensitivity of variable profit (hence willingness to invest) to exogenous changes in \( P \) and compare it to the sensitivity of variable profit to exogenous ‘demand shocks’ (e.g., changes in market size).

A change in \( P \) has an indirect as well as a direct effect on variable profit, via the demand function. Suppose that the demand function is log-linear rather than linear:

\[ Q = NP^{-\beta} \]

or

\[ \ln Q = \ln N - \beta \ln P \]

where \( N \) is the number of consumers and \( \beta \) is the elasticity of demand. I assume that the elasticity of \( Q \) with respect to \( N \) is one, for example, a 10% increase in disease incidence would cause quantity demanded to increase 10%, holding price constant.

Then we may write

\[ \ln \Pi_V = \ln(P - m) + \ln Q \]
\[ = \ln(P - m) + \ln N - \beta \ln P \]
The elasticity of variable profit with respect to the number of consumers is one. The elasticity of variable profit with respect to price is

\[ \frac{\delta \ln \Pi_v}{\delta \ln P} = \frac{P}{P - m} - \beta \]

\[ = \frac{1}{1 - (m/P)} - \beta \]

Suppose, for a moment, that the demand for pharmaceuticals were completely inelastic: \( \beta = 0 \). In this case

\[ \frac{\delta \ln \Pi_v}{\delta \ln P} = \frac{1}{1 - (m/P)} > 1 = \frac{\delta \ln \Pi_v}{\delta \ln N} \]

The elasticity of variable profit with respect to price is greater than one, and is therefore greater than the elasticity of variable profit with respect to the number of consumers. 'If demand were completely inelastic, variable profit would be more sensitive to price than it is to market size.' A reduction in the number of consumers reduces cost as well as revenue, whereas a reduction in price reduces only revenue.

To calculate the elasticity of variable profit with respect to price when demand is completely inelastic, we require only an estimate of \((m/P)\), the reciprocal of the price–cost margin. Hughes et al. (2002, p. 6), citing Grabowski and Vernon (1992, 1996), note that 'once multiple generic manufacturers enter [the market following patent expiration], they typically price their drugs at discounts of 70 to 90 percent below the incumbent’s price prior to entry. This observation implies that the ratio of price to marginal cost for branded drugs with patent protection is about 6:1.' If \((m/P) = 1/6\), the elasticity of variable profit with respect to price when demand is completely inelastic is \(1/(1 - (1/6)) = 1.20\).

However, other evidence suggests that the mean ratio of generic price to branded price is much higher. Data from the 2002 Medical Expenditure Panel Survey indicate that the mean price of generic prescriptions was $30 \( (N = 124,555) \), and that the mean price of branded prescriptions was $75 \( (N = 189,312) \); hence, the ratio of mean prices was 0.40. However, this ratio compares prices of different products, for example, antibiotics and cardiovascular drugs. We can calculate the mean percentage differential of the prices of generic and branded versions of the same product by estimating the following model:

\[ \ln P_{ij} = \delta \text{ GENERIC}_{ij} + \alpha_j + \varepsilon_{ij} \]

where

\[ P_{ij} = \text{the price of the } i\text{th prescription for product } j \]

\[ \text{GENERIC}_{ij} = 1 \text{ if the } i\text{th prescription for product } j \text{ is a generic prescription} \]

\[ = 0 \text{ if the } i\text{th prescription for product } j \text{ is a branded prescription} \]

\[ \alpha_j = \text{a fixed effect for product } j, \text{ where a product is defined by active ingredient(s), dosage form, strength, and route of administration}^{4} \]

The estimate of the within-product price differential \( \delta \), based on data on 258,276 prescriptions for 2235 products, is \(-0.317 \text{ (t-statistic } = 65.3)\). This implies that the mean ratio of the price of a generic prescription to the price of a branded prescription for the same product is

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4 Product definitions and designation as branded or generic are determined by Multum, Inc.
0.73 (= \exp(-0.317)). If \((m/P) = 0.40\), the elasticity of variable profit with respect to price when demand is completely inelastic is 1.68; if \((m/P) = 0.73\), it is 3.68.

Some evidence indicates that the demand for pharmaceuticals is completely inelastic: a study by Caves et al. (1991) found that the total amount sold of a drug in both generic and brand-name forms did not increase after generic entry.\(^5\) Moreover, as Folland et al. (2001) argue, insurance reduces the price elasticity, and prescription drug insurance coverage has been rising. According to an April 2000 Department of Health & Human Services Report to the President,\(^6\) in 1998 only 27 cents out of every dollar of pharmaceutical expenditure was paid for out of pocket by households; 53 cents was paid by private insurance and the remainder was paid by Medicaid and other sources (Figures 2–16).

However, evidence from several studies suggests that the elasticity of demand for pharmaceuticals is positive, but not large. One of these was the Health Insurance Experiment (HIE), which randomized people to various insurance plans that differed in their co-payments and deductibles. The HIE yielded an elasticity of prescription drug expenditures of 0.27, implying that a 10% reduction in the price of drugs would increase spending by 2.7%. Lillard et al. (1999) observed a similar response (0.25) among the elderly.\(^7\) Goldman et al. (2002) stated that ‘overall, the literature suggests elasticities that range between 0.20 and 0.35.’

If \((m/P) = 1/6\), and the demand elasticity is 0.20, the elasticity of variable profit with respect to price happens to be equal to unity, the same as the elasticity of variable profit with respect to the number of consumers:

\[
\frac{\delta \ln \Pi_v}{\delta \ln P} = \frac{1}{1 - (m/P)} - \beta = \frac{1}{1 - (1/6)} - 0.20 = 1
\]

If the demand elasticity is 0.35, the elasticity of variable profit with respect to price equals 0.85, which is lower than the elasticity of variable profit with respect to the number of consumers, but not by much. This suggests that the elasticity of variable profit with respect to price is likely to be similar to the elasticity of variable profit with respect to the number of consumers. Hence, an estimate of the effect of the number of consumers on investment may also be considered as an approximate estimate, or forecast, of the effect of price on investment.

3 EVIDENCE ABOUT THE EFFECT OF MARKET SIZE ON PHARMACEUTICAL INNOVATION

To estimate the effect of market size on pharmaceutical innovation, there must be observable, exogenous variation in market size (e.g., disease incidence) that can be linked to innovation measures. Estimates of the incidence (i.e., the annual number of new cases)\(^8\) of 365 conditions

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\(^5\) A choice-modeling experiment performed by Merino-Castelló (2003, p. 31) also provided evidence of low price elasticity of demand for pharmaceuticals.


\(^7\) The estimated elasticity is based on Goldman et al.’s (2002) calculations, using the demand response shown in Table IV of Lillard et al. (1999) for elderly with Medicare only. Using information from the Medicare Current Beneficiary Survey (MCBS), they assumed that the average coinsurance rate for these elderly is 100% without insurance and 45% with insurance. The 45% average coinsurance rate is based on our calculation of observed coinsurance rates (out-of-pocket expenditures divided by total expenditures) for people with private supplemental drug coverage in the 1995 MCBS.

\(^8\) This measure differs from ‘prevalence’, which is the cumulative number of people currently affected.
TABLE I Twenty-five conditions with highest US incidence.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent</th>
<th>Incidence rate</th>
<th>US people</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diarrhea</td>
<td>100.00</td>
<td>1 in 1</td>
<td>272 million</td>
<td>almost 100% annually (NIDDK)</td>
</tr>
<tr>
<td>2. Common headache</td>
<td>90.00</td>
<td>1 in 1</td>
<td>244.8 million</td>
<td>approximately 90%; almost everyone gets some each year.</td>
</tr>
<tr>
<td>3. Dental caries</td>
<td>55.57</td>
<td>1 in 2</td>
<td>151.2 million</td>
<td>2,534,161 annual cases in Victoria 1996 (DHS-VIC)</td>
</tr>
<tr>
<td>5. Flu</td>
<td>36.00</td>
<td>1 in 3</td>
<td>97.9 million</td>
<td>36 per 100 (NHIS96); 35 million annually up to 50 million annually (NIAID/CDC); 10–20% yearly (NIAID)</td>
</tr>
<tr>
<td>6. Food poisoning</td>
<td>27.94</td>
<td>1 in 3</td>
<td>76 million</td>
<td>About 76 million cases annually in US (NIDDK)</td>
</tr>
<tr>
<td>7. Common cold</td>
<td>22.79</td>
<td>1 in 4</td>
<td>62 million</td>
<td>62 million cases (NIAID); 23.6 per 100 (NHIS96); estimated 1 billion colds in the US annually; Children get 6–10 yearly, adults 2–4 yearly; over 60’s less than 1 a year.</td>
</tr>
<tr>
<td>8. Mental illness</td>
<td>22.10</td>
<td>1 in 4</td>
<td>60.1 million</td>
<td>About 22.1% of American adults annually or 44.3 million people (NIMH)</td>
</tr>
<tr>
<td>9. Injury</td>
<td>21.69</td>
<td>1 in 4</td>
<td>59 million</td>
<td>59 million cases (IOM)</td>
</tr>
<tr>
<td>10. Hives</td>
<td>15.00</td>
<td>1 in 6</td>
<td>40.8 million</td>
<td>About 15% Americans each year (NWHIC)</td>
</tr>
<tr>
<td>11. Chronic Sinusitis</td>
<td>12.83</td>
<td>1 in 7</td>
<td>34.9 million</td>
<td>34.9 million cases per year in the US 1994 (US Government Statistics)</td>
</tr>
<tr>
<td>12. Depressive disorders</td>
<td>6.91</td>
<td>1 in 14</td>
<td>18.8 million</td>
<td>Estimated 18.8 million American adults annually (NIMH)</td>
</tr>
<tr>
<td>13. Sexually transmitted diseases</td>
<td>5.62</td>
<td>1 in 17</td>
<td>15.3 million</td>
<td>15.3 million annual cases (NIAID)</td>
</tr>
<tr>
<td>14. Acute bronchitis</td>
<td>4.60</td>
<td>1 in 21</td>
<td>12.5 million</td>
<td>4.6 per 100 (NHIS96: acute bronchitis); 14.2 million cases annually</td>
</tr>
<tr>
<td>15. Iron deficiency anemia</td>
<td>4.12</td>
<td>1 in 24</td>
<td>11.2 million</td>
<td>187,979 annual cases in Victoria 1996 (DHS-VIC); 20% women of childbearing age; 2% adult men (NWHIC)</td>
</tr>
<tr>
<td>16. Social phobia</td>
<td>3.70</td>
<td>1 in 27</td>
<td>10.1 million</td>
<td>3.7% adults annually (NIMH)</td>
</tr>
<tr>
<td>17. Traveler’s diarrhea</td>
<td>3.68</td>
<td>1 in 27</td>
<td>10 million</td>
<td>Estimated 10 million (DBMD)</td>
</tr>
<tr>
<td>18. Enteroviruses</td>
<td>3.68</td>
<td>1 in 27</td>
<td>10 million</td>
<td>Estimated 10–15 million cases annually in US (DVRD)</td>
</tr>
<tr>
<td>19. Post-traumatic stress disorder</td>
<td>3.60</td>
<td>1 in 27</td>
<td>9.8 million</td>
<td>3.6% adults annually (NIMH)</td>
</tr>
<tr>
<td>20. Acute urinary conditions</td>
<td>3.09</td>
<td>1 in 32</td>
<td>8.4 million</td>
<td>8.405 million new conditions (NIDDK)</td>
</tr>
<tr>
<td>21. Acute nonulcer dyspepsia</td>
<td>3.01</td>
<td>1 in 33</td>
<td>8.2 million</td>
<td>8.2 million new cases (1988/NIDDK)</td>
</tr>
<tr>
<td>22. Generalized anxiety disorder</td>
<td>2.80</td>
<td>1 in 35</td>
<td>7.6 million</td>
<td>2.8% of the adult US population (NIMH)</td>
</tr>
<tr>
<td>23. Middle ear infection</td>
<td>2.57</td>
<td>1 in 38</td>
<td>7 million</td>
<td>7 million annually</td>
</tr>
<tr>
<td>24. Occupational injuries</td>
<td>2.32</td>
<td>1 in 43</td>
<td>6.3 million</td>
<td>6.3 million workers in 1994 (CDC-OC)</td>
</tr>
<tr>
<td>25. Obsessive-compulsive disorder</td>
<td>2.30</td>
<td>1 in 43</td>
<td>6.3 million</td>
<td>2.3% adults annually (NIMH)</td>
</tr>
</tbody>
</table>

have been compiled and posted on the wrongdiagnosis.com website. In most cases, the incidence rates refer to the US or other industrialized nations. Data for the top 25 conditions are shown in Table I.

9 http://www.wrongdiagnosis.com/lists/incid.htm
Although these data are potentially useful, they may be subject to several limitations. First, they were derived from a variety of sources, covering different regions and time periods, and may not be directly comparable. A second and perhaps greater concern is that reported incidence may not be exogenous with respect to the availability of treatments. An increase in available treatments for a disease may lead to greater public and professional awareness of it (e.g., due to more promotion and advertising by drug companies), and therefore to higher reported incidence.

There is one important set of diseases – different forms of cancer – for which reliable, systematic incidence data are available, and where the potential for ‘reverse causality’ (from treatment availability to incidence) is likely to be quite limited. Reliable data on the incidence of cancer, by cancer site (e.g., breast and prostate), are available from GLOBOCAN. The GLOBOCAN 2002 database provides estimates of the incidence and prevalence of, and mortality from, 27 cancers for all countries in the world in 2002. The database has been built up using the huge amount of data available in the Descriptive Epidemiology Group of the International Agency for Research on Cancer (IARC), part of the World Health Organization. Incidence data are available from cancer registries.

If drugs were the only or primary treatment for cancer, or if drugs were often used to diagnose cancer, as well as to treat it, the possibility of reverse causality would be greater. But drugs are not the only cancer treatment: as noted by the British Columbia Cancer Agency, surgery and radiation therapy, as well as cancer drugs, ‘are all proven to cure cancer, extend life, or improve quality of life.’11 Also, data contained in the National Library of Medicine’s Unified Medical Language System Metathesaurus indicate that only 0.4% of cancer drugs are used to diagnose cancer. The vast majority (98.7%) are used to treat cancer; 0.9% are used to prevent cancer.

I will examine the relationship, across cancer sites, between cancer incidence and two different measures of pharmaceutical innovation. The first is the number of distinct chemotherapy regimens for treating the cancer site. The second is the number of articles published in scientific journals pertaining to drug therapy for that cancer site.

Cancer Care Ontario (CCO) publishes lists of chemotherapy regimens grouped by disease site. The regimens are categorized according to the recommendations of the respective CCO Disease Site Group. I will use the number of core chemotherapy regimens for a disease site. A core therapy is defined as a ‘standard therapy; a regimen widely used by most Regional Cancer Centres in this disease site.’ Data on the number of new cases in Canada in 2002, by cancer site, were obtained from GLOBOCAN 2002. Data on the estimated number of new cases in the US in 2000, by cancer site, were obtained from the SEER Cancer Statistics Review, 1975–2002.

Data on 18 cancer sites, listed in descending order of incidence in Canada, are shown in Table II. In both Canada and the US, the top four cancer sites – lung, breast, prostate, and colorectal – account for about two-thirds of all cases. They account for 46% of core chemotherapy regimens. Figure 1 plots the log of the number of core chemotherapy regimens for a site against the log of the number of cases in Canada in 2002. Statistics from the regression

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10 Some of the estimates are based on household data (i.e., on self-reported medical conditions), whereas others are based on surveys of medical providers.


13 Other categories include ‘local regimens’ (regimens not widely used; used by fewer than four regional cancer centers) and ‘emergent regimens’ (regimens which have not yet been accepted as standard regimens).

TABLE II  Cancer incidence and number of core chemotherapy regimens, by site.

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of cases in Canada in 2002</th>
<th>Number of core chemotherapy regimens</th>
<th>Number of cases in the US in 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>20,648</td>
<td>11</td>
<td>164,100</td>
</tr>
<tr>
<td>Breast</td>
<td>19,540</td>
<td>21</td>
<td>182,800</td>
</tr>
<tr>
<td>Prostate</td>
<td>17,900</td>
<td>11</td>
<td>180,400</td>
</tr>
<tr>
<td>Colorectal</td>
<td>17,708</td>
<td>3</td>
<td>130,200</td>
</tr>
<tr>
<td>Lymphoma – Non-Hodgkins</td>
<td>5671</td>
<td>11</td>
<td>54,900</td>
</tr>
<tr>
<td>Renal</td>
<td>3858</td>
<td>1</td>
<td>31,200</td>
</tr>
<tr>
<td>Uterine/Sarcoma</td>
<td>3643</td>
<td>1</td>
<td>36,100</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3636</td>
<td>16</td>
<td>30,800</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3585</td>
<td>4</td>
<td>47,700</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3277</td>
<td>1</td>
<td>28,300</td>
</tr>
<tr>
<td>Gastric</td>
<td>3132</td>
<td>4</td>
<td>21,500</td>
</tr>
<tr>
<td>Ovary</td>
<td>2661</td>
<td>3</td>
<td>23,100</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>2356</td>
<td>1</td>
<td>16,500</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1855</td>
<td>3</td>
<td>13,600</td>
</tr>
<tr>
<td>Cervix</td>
<td>1502</td>
<td>2</td>
<td>12,800</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1378</td>
<td>3</td>
<td>12,300</td>
</tr>
<tr>
<td>Lymphoma – Hodgkins</td>
<td>838</td>
<td>2</td>
<td>7400</td>
</tr>
<tr>
<td>Testis</td>
<td>775</td>
<td>3</td>
<td>6900</td>
</tr>
</tbody>
</table>

The elasticity of the log of the number of core chemotherapy regimens on the log of the number of cases in Canada in 2002 are:

**Regression statistics**

<table>
<thead>
<tr>
<th></th>
<th>Multiple $R$</th>
<th>$R^2$</th>
<th>Adjusted $R$ Square</th>
<th>Standard error</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.550452</td>
<td>0.302998</td>
<td>0.259435</td>
<td>0.84812</td>
<td>18</td>
</tr>
</tbody>
</table>

**ANOVA**

<table>
<thead>
<tr>
<th></th>
<th>df</th>
<th>SS</th>
<th>MS</th>
<th>$F$</th>
<th>Significance $F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1</td>
<td>5.003104</td>
<td>5.003104</td>
<td>6.955448</td>
<td>0.017927</td>
</tr>
<tr>
<td>Residual</td>
<td>16</td>
<td>11.50892</td>
<td>0.719307</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>16.51202</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Coefficients</th>
<th>Standard Error</th>
<th>$t$-stat</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$-3.06576$</td>
<td>1.651987</td>
<td>$-1.8558$</td>
<td>0.081997</td>
</tr>
<tr>
<td>ln(CA cases)</td>
<td>0.525554</td>
<td>0.199276</td>
<td>2.637318</td>
<td>0.017927</td>
</tr>
</tbody>
</table>

The elasticity of the number of chemotherapy regimens with respect to the number of cases is 0.53, and the estimate is significantly different from zero ($P = 0.018$). A 10% increase
in the number of cases is associated with a 5.3% increase in the number of chemotherapy regimens.15

Now I will examine the relationship, across cancer sites, between cancer incidence and the number of articles published in scientific journals pertaining to drug therapy for that cancer site. Data on the latter were obtained by searching MEDLINE (Medical Literature Analysis and Retrieval System Online), the U.S. National Library of Medicine’s (NLN) premier bibliographic database of biomedical citations and abstracts. The subject scope of MEDLINE is biomedicine and health, broadly defined to encompass those areas of the life sciences, behavioral sciences, chemical sciences, and bioengineering needed by health professionals and others engaged in basic research and clinical care, public health, health policy development, or related educational activities. It contains approximately 13 million references to journal articles that appeared in over 4800 journals published in the US and more than 70 other countries primarily from 1966 to the present.16

References to articles are indexed with terms from NLN’s controlled vocabulary, MeSH (Medical Subject Headings). MeSH is the National Library of Medicine’s controlled vocabulary thesaurus. It consists of 22,568 descriptors in a hierarchical structure that permit searching at various levels of specificity. The MESH Section staff continually revises and updates the MeSH vocabulary. Staff subject specialists are responsible for areas of the health sciences in which they have knowledge and expertise. In addition to receiving suggestions from indexers and others, the staff collect new terms as they appear in the scientific literature or in emerging areas of research; define these terms within the context of existing vocabulary; and recommend their addition to MeSH.

15 The elasticity is virtually identical when we use the log number of cases in the US in 2000 instead of the log number of cases in Canada in 2002. US and Canadian incidence across cancer sites is extremely highly correlated.16 The great majority of journals are selected for MEDLINE based on the recommendation of the Literature Selection Technical Review Committee, an NIH-chartered advisory committee of external experts analogous to the committees that review NIH grant applications. The majority of the publications covered in MEDLINE are scholarly journals; a small number of newspapers, magazines, and newsletters considered useful to particular segments of NLN’s broad user community are also included. Citations for MEDLINE are created by the NLN, international partners, and collaborating organizations.
At the highest (most general) level of the MeSH hierarchical structure are the following 15 headings:

1. Anatomy [A]
2. Organisms [B]
3. Diseases [C]
4. Chemicals and Drugs [D]
5. Analytical, Diagnostic and Therapeutic Techniques and Equipment [E]
6. Psychiatry and Psychology [F]
7. Biological Sciences [G]
8. Physical Sciences [H]
9. Anthropology, Education, Sociology and Social Phenomena [I]
10. Technology and Food and Beverages [J]
11. Humanities [K]
12. Information Science [L]
13. Persons [M]
14. Health Care [N]
15. Geographic Locations [Z]

We can search MEDLINE for all articles pertaining to particular diseases, and for articles specifically pertaining to drug treatment of those diseases. For example, the search string ‘exp leukemia’ identifies all articles in MEDLINE that pertain to any form of leukemia, and the search string ‘exp leukemia/dt’ identifies all articles in the database that pertain to drug therapy for any form of leukemia.

The MEDLINE data we have described refer to publication; my objective is to measure innovation. I think that publication is closely related to, and a good indicator of, innovation. The majority of the publications covered in MEDLINE are scholarly journals, and novelty is generally a necessary (but not sufficient) condition for publication in such journals. However, the novelty criteria used by scholarly journals undoubtedly differ from those used by other authorities (e.g., the US Patent and Trademark Office or CCO’s Disease Site Groups).

Table III shows data on incidence in 2002, by region (less vs. more developed), and number of MEDLINE article citations, for 25 cancer sites as defined in GLOBOCAN. I calculated both total and drug-therapy article cites for each cancer site, from which non-drug cites may also be computed:

\[
\text{TOTAL\_CITE}_i = \text{the total number of MEDLINE articles pertaining to cancer site } i \\
\text{DRUG\_CITE}_i = \text{the number of MEDLINE articles pertaining to drug therapy for cancer site } i \\
\text{NONDRUG\_CITE}_i = \text{other MEDLINE articles pertaining to cancer site } i \\
= \text{TOTAL\_CITE}_i - \text{DRUG\_CITE}_i
\]

17 Novelty is also a necessary condition for patenting. A searchable US patents database exists, and some investigators have used patent counts and citations as innovation indicators. However, the US patent classification system is much cruder than the MeSH classification system with respect to medical innovation and is inadequate for our purposes.
Using the data in Table III, I estimated the following four models:

Model 1: \( \ln \text{DRUG\_CITES}_i = \alpha_1 + \beta_{DW} \ln \text{INC\_WORLD}_i + e_i \)

Model 2: \( \ln \text{NONDRUG\_CITES}_i = \alpha_2 + \beta_{NW} \ln \text{INC\_WORLD}_i + e_i \)

Model 3: \( \ln \text{DRUG\_CITES}_i = \alpha_3 + \beta_{DM} \ln \text{INC\_MORE}_i + \beta_{DL} \ln \text{INC\_LESS}_i + e_i \)

Model 4: \( \ln \text{NONDRUG\_CITES}_i = \alpha_4 + \beta_{NM} \ln \text{INC\_MORE}_i + \beta_{NL} \ln \text{INC\_LESS}_i + e_i \)

where

\( \text{INC\_WORLD}_i = \text{the incidence of cancer at site } i \text{ throughout the world} \)

\( \text{INC\_MORE}_i = \text{the incidence of cancer at site } i \text{ in the more developed region} \)

\( \text{INC\_LESS}_i = \text{the incidence of cancer at site } i \text{ in the less developed region} \)

Estimates of these equations are shown in Table IV. Estimates of model 1 indicate that the elasticity of MEDLINE drug cites with respect to cancer incidence throughout the world is 0.60, and is significantly different from zero. Estimates of model 2 indicate that the elasticity of MEDLINE non-drug cites with respect to cancer incidence throughout the world is virtually identical, and is also significantly different from zero. There is more publication (presumably indicating more research and innovation) related to cancers with higher incidence. A 10% increase in cancer incidence is associated with a 6% increase in both the number of drug-therapy publications and non-drug therapy publications.
TABLE IV  Estimates of the relationship between cancer incidence and the number of drug and non-drug MEDLINE citations.

<table>
<thead>
<tr>
<th>Model</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>dep. Var.</td>
<td>ln DRUG–CITES_i</td>
<td>ln DRUG–CITES_i</td>
<td>ln DRUG–CITES_i</td>
<td>ln DRUG–CITES_i</td>
</tr>
<tr>
<td>ln INC.–WORLD_i</td>
<td>0.597</td>
<td>0.598</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard error</td>
<td>0.210</td>
<td>0.138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-stat</td>
<td>2.850</td>
<td>4.330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.009</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln INC.–MORE_i</td>
<td></td>
<td></td>
<td>0.670</td>
<td>0.433</td>
</tr>
<tr>
<td>Standard error</td>
<td></td>
<td></td>
<td>0.209</td>
<td>0.145</td>
</tr>
<tr>
<td>t-stat</td>
<td></td>
<td></td>
<td>3.200</td>
<td>3.000</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>ln INC.–LESS_i</td>
<td></td>
<td></td>
<td></td>
<td>−0.065</td>
</tr>
<tr>
<td>Standard error</td>
<td></td>
<td></td>
<td></td>
<td>0.222</td>
</tr>
<tr>
<td>t-stat</td>
<td></td>
<td></td>
<td></td>
<td>−0.290</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>0.774</td>
</tr>
</tbody>
</table>

Models 3 and 4 distinguish between incidence in the more developed and less developed regions. Model 3 indicates that the number of drug-therapy publications is related to incidence in the more-developed region but not to incidence in the less-developed region. Model 4 indicates that the number of non-drug therapy publications is also related to incidence in the more-developed region but not to incidence in the less-developed region, although the more- vs. less-developed difference between the sensitivity of the number of drug-therapy publications (\(\beta_{DM} - \beta_{DL} = 0.73\)) is almost three times as large as the more- vs. less-developed difference between the sensitivity of the number of non-drug-therapy publications (\(\beta_{NM} - \beta_{NL} = 0.27\)).

I think that the most plausible explanation for the lack of a relationship between the incidence in developing countries and the amount of pharmaceutical innovation has been weak or nonexistent incentives for firms to develop medicines for diseases primarily affecting people in developing countries. Although the size of the developing-region market is large, the prices manufacturers expect to receive in this market are probably very low.\(^{18}\)

4 DISCUSSION

I performed two analyses of the relationship, across cancer sites, between cancer incidence and pharmaceutical innovation, using two different measures of the latter: the number of distinct chemotherapy regimens for treating the cancer site and the number of articles published in scientific journals pertaining to drug therapy for that cancer site. Both analyses indicated that the amount of pharmaceutical innovation increases with disease incidence. The elasticity of the number of chemotherapy regimens with respect to the number of cases is 0.53. The elasticity of MEDLINE drug cites with respect to cancer incidence throughout the world is 0.60. These estimates are quite close, despite the fact that the innovation measures used are quite different.

If the ratio of price to marginal cost for branded drugs with patent protection is about 6:1, as some evidence suggests, then the elasticity of variable profit with respect to price is likely to be

\(^{18}\) Prices of other (non-drug) medical treatments (e.g., hospital care) are also undoubtedly lower in the developing region than they are in the developed region. But the ratio of the expected drug price to the price of other medical treatments may be lower in the developing region (due to the low marginal cost of drugs). This could explain why (\(\beta_{DM} - \beta_{DL}\)) is almost three times as large as (\(\beta_{NM} - \beta_{NL}\)).
similar to the elasticity of variable profit with respect to the number of consumers. This suggests that the elasticity of innovation with respect to price is similar to the elasticity of innovation with respect to market size, which I estimate to be in the 0.53–0.60 range. This estimate is very consistent with Giaccotto et al.’s (2005) estimate (0.583) of the elasticity of pharmaceutical industry R&D with respect to the real price of pharmaceuticals. That study employed time series econometric techniques to explain R&D growth rates using industry-level data from 1952 to 2001.

A recent paper by Abbott and Vernon (2005) suggests that the elasticity of innovation with respect to price may be somewhat higher. Using Monte Carlo techniques, they model how future price controls in the US will impact early-stage product development decisions within the context of a net present value framework that appropriately reflects the uncertainty associated with R&D project technical success, development costs, and future revenues. Using partial-information estimators calibrated with the most contemporary clinical and economic data available, they estimate that cutting prices by 40–5% in the US will lead to between 30 and 60% fewer R&D projects being undertaken (in early-stage development). The elasticity of innovation with respect to price is therefore in the 0.67–1.33 range. Since evidence from the 2002 MEPS suggests that the ratio of price to marginal cost is lower than 6:1, the elasticity of variable profit with respect to price is likely to be greater than the elasticity of variable profit with respect to the number of consumers; hence, my estimates seem compatible with Abbott and Vernon’s.

My estimates, and those obtained by other authors using very different approaches, imply that importation would be likely to significantly reduce the amount of pharmaceutical innovation. It would also be likely to reduce employment in the US pharmaceutical industry. We can get a rough assessment of the employment impact of reduced pharmaceutical innovation by examining the relationship, across pharmaceutical companies, between the number of innovations and the number of employees. I defined the number of innovations by a company as the number of FDA-approved active ingredients contained in products sold by the company that are not contained in any other company’s products.19 Data on the number

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19 This measure was constructed from the Multum Lexicon database (http://www.multum.com/Lexicon.htm).
of innovations by, and number of employees of, 14 selected major pharmaceutical companies are shown in Table V. Figure 2 plots the log of the number of company employees against the log of the number of innovations. The relationship depicted is highly statistically significant: the elasticity of employment with respect to the number of innovations is 0.71 ($p < 0.001$).

References


