Pharmaceutical innovation and the burden of disease in developing and developed countries

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Abstract

I perform three different analyses of the relationship across diseases between pharmaceutical innovation and the burden of disease in developed and developing countries. First, I examine the relationship between the number of disability-adjusted life-years (DALYs) attributable to a disease in 2001, by region, and the number of drugs that have been developed to treat the disease and that are sold in the U.S. Second, I examine the relationship between the number of DALYs attributable to a disease in 2001, and the number of drugs launched to treat the disease in approximately 50 countries during the period 1982-2002. Third, I examine the relationship between cancer incidence (the number of people diagnosed with a particular form of cancer), and the number of articles published in scientific journals pertaining to drug therapy for that form of cancer.

All three analyses indicate that the amount of pharmaceutical innovation is positively related to the burden of disease in developed countries but not to the burden of disease in developing countries. The amount of other medical innovation also appears to be positively related to the burden of disease in developed countries but not to the burden of disease in developing countries, although the developed-vs.-developing difference is smaller than in the case of pharmaceutical innovation.

The most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation is that incentives for firms to develop medicines for diseases primarily afflicting people in developing countries have been weak or nonexistent. Economic research has demonstrated that investment in R&D is greatly affected by incentives that are offered for R&D. To increase the rate of development of drugs for diseases primarily afflicting people in developing countries, incentives for developing these drugs must be strengthened. The establishment of purchase commitment funds may be the most efficient way to stimulate the development and production of these drugs.

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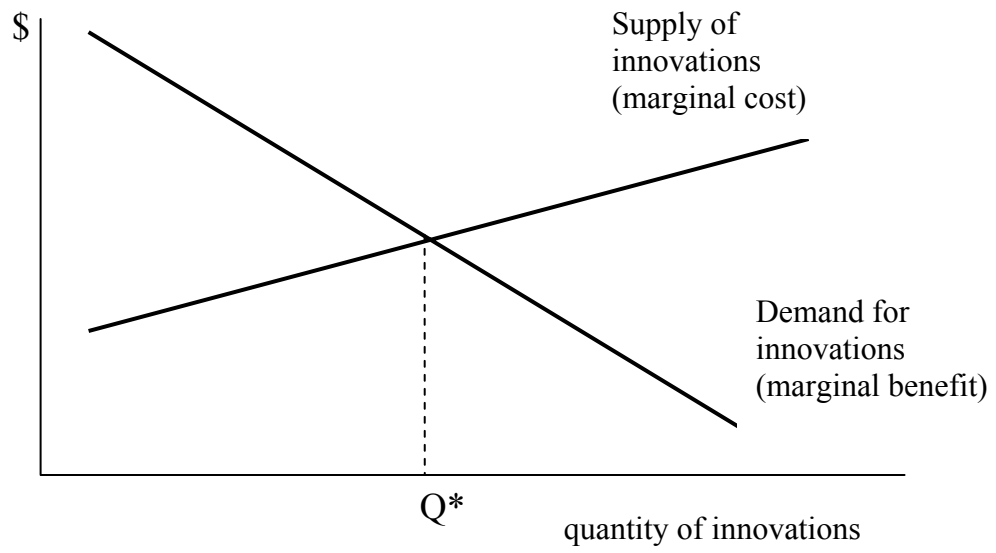
In this paper I will examine the relationship, across diseases, between the magnitude of the burden of a disease, total and by WHO Region, and several alternative measures of pharmaceutical innovation related to the treatment of the disease.

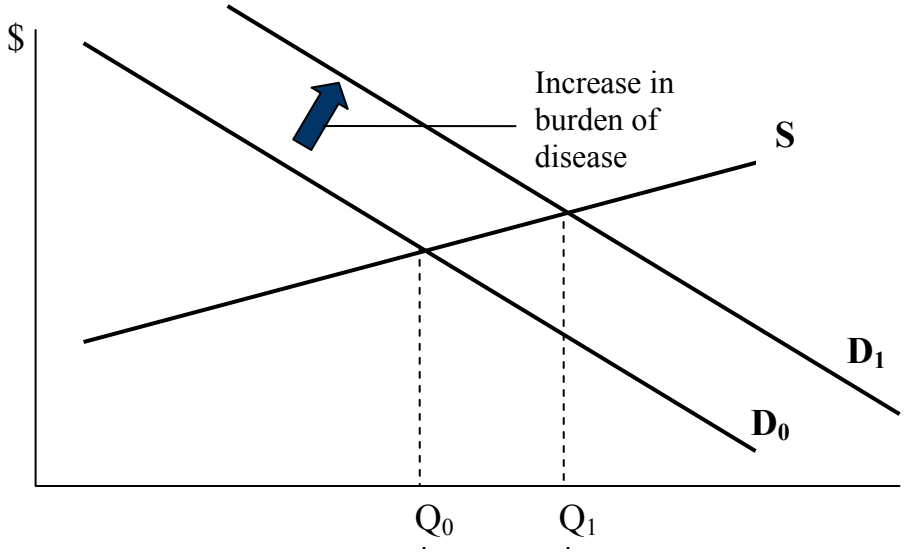
Theoretical considerations

Suppose that there is a positive relationship across diseases between the number of treatments for a disease and the perceived burden of disease: $T_i = f(P_i)$, where T_i = the number of treatments for disease i; P_i = the perceived burden of disease i; and $f' > 0$. This equation may be interpreted as a reduced-form market equilibrium equation resulting from a simple structural model of the market for pharmaceutical innovations. The market for pharmaceutical innovations may be represented graphically as follows:



The equilibrium quantity of innovations (Q*) is determined by both the demand for (marginal benefit of) innovations and the supply (marginal cost) of innovations.

An increase in the burden of disease increases the marginal (social) benefit of innovations, but there is no reason to believe that it affects the marginal cost of innovation. Hence, it increases the equilibrium quantity of innovations:



In principle, the demand for innovations, or treatment, should depend on the burden of *untreated* disease. However, often we only have data about the burden of *treated* illness.[1] An increase in the number of treatments presumably reduces the ratio of the burden of treated disease to the burden of untreated disease.[2] Therefore, the slope of the relationship between the number of innovations and the burden of treated disease is likely to be an underestimate of the slope of the relationship between the number of innovations and the burden of untreated disease.

I will perform three different analyses of the relationship between pharmaceutical innovation and the burden of disease. In Section I, I will examine the relationship between the number of disability-adjusted life-years (DALYs) attributable to a disease in 2001, and the number of drugs that have been developed to treat the disease and that are sold in the U.S., determined from an authoritative drug database, *Mosby's Drug Consult*.

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[1] I will examine data on both the burden of treated illness and the burden of untreated illness. The untreated burden of illness measure is the number of cancer cases, by type of cancer.

[2] I have shown in several papers that the introduction of new drugs reduces mortality and morbidity. See, for example, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," in *Measuring the Gains from Medical Research: An Economic Approach*, ed. by Kevin M. Murphy and Robert H. Topel (Chicago: University of Chicago Press, 2003), pp. 74-109.; "Sources of U.S. Longevity Increase, 1960-2001," *Quarterly Review of Economics and Finance* 44(3), pp. 369-389 (July 2004); "The impact of new drug launches on longevity: evidence from longitudinal disease-level data from 52 countries, 1982-2001," *International Journal of Health Care Finance and Economics*, forthcoming; and "Availability of new drugs and Americans' ability to work," *Journal of Occupational and Environmental Medicine*, forthcoming April 2005.

In Section II, I will examine the relationship between the number of DALYs attributable to a disease in 2001, and the number of drugs launched to treat the disease in approximately 50 countries during the period 1982-2002, determined from *IMS Drug Launches* database. In Section III, I will examine the relationship between disease incidence (the number of people diagnosed with the disease), and the number of articles published in scientific journals pertaining to drug therapy for that disease, determined from the *MEDLINE* database.

Each of these analyses has strengths and weaknesses. The first analysis uses the most reliable and complete classification of drugs by disease, but measures the number of drugs sold in the U.S. rather than globally. The second analysis measures the number of drugs launched in over 50 developed and developing countries, but only since 1982, and the classification of drugs is less reliable and complete than the classification used in the first analysis. Only the third analysis uses data on the burden of untreated illness, which is theoretically preferable. That analysis also includes an examination of the relationship between *other medical* (non-pharmaceutical) innovation and the burden of disease.

I. The relationship between the number of DALYs attributable to a disease and the number of drugs that have been developed to treat the disease and that are sold in the U.S.

A. Measurement

The burden of a disease will be measured by the number of disability-adjusted life-years (DALYs) attributable to the disease in 2001, as calculated by WHO.[3] The number of drugs that have been developed to treat the disease is determined from *Mosby's Drug Consult,* a compilation of the most current, complete, and unbiased information on prescription pharmaceuticals available today.[4] The information in Mosby's was obtained from the FDA, the Center for Medicare and Medicaid Services, pharmaceutical supplier catalogs, standard pharmacology texts, peer-reviewed medical journals, and other publicly available sources.

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[3] Unfortunately, similar data for previous years are not available.

[4] The prescribing information found in *Mosby's Drug Consult* is for prescription pharmaceuticals and except for a few selected non-prescription drugs those products available without a prescription will not be listed.

Data on estimated DALYs in 2001, by cause and region, are shown in Appendix Table 1. As shown in Figure 1, high-mortality developing countries account for 38% of the world's population but for 57% of total DALYs. Developed countries account for 22% of the world's population but for only 15% of total DALYs. DALYs per person are about twice as high in high-mortality developing countries as they are in the other two regions (where, surprisingly, DALYs per person are virtually equal).

Using *Mosby's Drug Consult,*[5] I attempted to identify all of the drugs currently available to treat as many of the diseases listed in Appendix Table 1 as possible. Mosby's Drug Consult contains full prescribing information for thousands of U.S.-approved pharmaceuticals indexed by generic name, trade name, international brand name, indication and drug class. I searched the "Indications for use" section of the Mosby's database for each of the diseases listed in Appendix Table 1.[6] Some of the diseases listed in Appendix Table 1 could not be found in the Mosby database—there was not a close match between the (most detailed) WHO disease name and the Mosby indications for use. In some cases, this may be because the WHO disease name (e.g. "ischaemic heart disease") refers to a broad set of diseases (indications).[7] These diseases will be omitted from the analysis. I don't think there is any reason to believe that omission of these diseases will bias estimates of the relationship between disease burden and availability of treatments in any particular direction.

The 59 WHO diseases included in the analysis are listed in Table 1, along with the Mosby indication(s) for use associated with each disease. In some cases (e.g. leprosy, meningitis, and stomach cancer), there was a one-to-one correspondence between the WHO disease name and the Mosby indication for use. In other cases, a single WHO disease corresponded to multiple Mosby indications. For example, there were 13 Mosby indications associated with the WHO disease "Lymphomas, multiple myeloma".

The drugs approved to treat the Mosby indication(s) associated with each of the 59 conditions are listed in Appendix Table 2. There are 554 distinct drugs. Some drugs are used to treat more than one of the 59 conditions; there are 874 disease-drug matches.

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[5] http://www.mosbysdrugconsult.com/

[6] Most, if not all, of these "Indications for use" are FDA-approved indications.

[7] Unfortunately, indications are not organized hierarchically (e.g. according to the International Classification of Diseases) in Mosby or other pharmaceutical databases.

At the beginning of the new drug approval process, the FDA classifies each drug as either a "priority-review drug"—a drug that offers "significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease"—or as a "standard-review drug"—a drug that "appears to have therapeutic qualities similar to those of one or more already marketed drugs." Table 2 shows the distribution of New Drug Applications approved by the FDA in calendar years 1990-2003, by "therapeutic potential" (priority- vs. standard-review) and "chemical type" (new molecular entity, new formulation, etc.). Forty-two percent of the new molecular entities approved during 1990-2003 were designated priority-review drugs.

Using unpublished data provided to me by the FDA pursuant to a request under the Freedom of Information Act, I determined whether each of the 554 distinct drugs associated with the 59 conditions were priority-review or standard-review drugs. Thirty-two percent (180) of the 554 distinct drugs associated with the 59 conditions were priority-review drugs. I will also examine the relationship, across diseases, between the magnitude of the burden of a disease, total and by WHO Region, and the number of priority-review drugs that have been developed to treat the disease.

Table 3 presents the key data for the 59 WHO diseases included in the analysis. The first four columns of numbers show the number of DALYs, total and by region, reproduced from Appendix Table 1. The last two columns show the total number of drugs and the number of priority-review drugs for each disease.

B. Econometric issues

To examine the relationship between disease burden and number of drugs, one must consider the issue of the functional form of the relationship. Two simple functional forms are linear and log-linear. The (linear) relationship between world DALYs and number of drugs is shown in Figure 2a; the (log-linear) relationship between log(world DALYs) and log(number of drugs) is shown in Figure 2b. Both figures indicate that there is a significant positive relationship across diseases between world DALYs in 2001 and the number of drugs in 2004. However, due to the skewness of the distributions of diseases with respect to both number of DALYs and number of drugs—a small number of diseases account for a large share of DALYs and drugs—the log-linear relationship

appears to be more appropriate. The log-linear residuals appear to be "better-behaved", i.e. closer to normally distributed. I will therefore proceed under the assumption that the relationship between the "perceived burden" of a disease and the number of drugs for the disease is log-linear, of the form

$$T_i = \exp(\alpha)\, P_i^{\beta} \qquad (1)$$

where

T_i = the number of treatments for disease i
P_i = the perceived burden of disease i.

Taking the logarithm of eq. (1),

$$\ln T_i = \alpha + \beta \ln P_i \qquad (2)$$

Suppose that the perceived burden of disease i is the weighted sum of DALYs due to that disease in different regions:

$$P_i = DEV_i + \theta_L\, LMD_i + \theta_H\, HMD_i \qquad (3)$$

where

DEV_i = the number of DALYs due to disease i in the developed region
LMD_i = the number of DALYs due to disease i in the low-mortality developing region
HMD_i = the number of DALYs due to disease i in the high-mortality developing region

θ_L and θ_H represent the "weight" DALYs in low-mortality and high-mortality developing regions are given, relative to the weight DALYs in the developed region are given, in the perceived burden of disease. For example, if $\theta_H = 0.5$, that indicates that DALYs in the high-mortality developing region are given half as much weight as DALYs in the developed region in the perceived burden of disease.

Substituting eq. (3) into eq. (1),

$$T_i = \exp(\alpha)\, [DEV_i + \theta_L\, LMD_i + \theta_H\, HMD_i]^{\beta} \qquad (4)$$

This model may be estimated via nonlinear least-squares (NLS). One can also substituting eq. (3) into eq. (2), which yields

$$\ln T_i = \alpha + \beta \ln [DEV_i + \theta_L LMD_i + \theta_H HMD_i] \quad (5)$$

Eq. (5) may be approximated by the following relationship, which may be estimated via ordinary least-squares (OLS):

$$\ln T_i = \alpha + \beta \ln WORLD_i + \theta_L' (LMD_i / WORLD_i) + \theta_H' (HMD_i / WORLD_i) \quad (6)$$

where $WORLD_i = DEV_i + LMD_i + HMD_i$ = the (unweighted) sum of DALYs in all three regions, $\theta_L' = (\beta \theta_L)$, and $\theta_H' = (\beta \theta_H)$. While OLS estimation is usually preferable to NLS estimation, in our case there is a good reason to prefer NLS estimation. Sixteen of the 59 diseases had zero priority-review drugs. OLS estimation of eq. (6) requires exclusion of these 16 diseases (since the log of zero is not defined), which could bias the estimates, due to censoring based on the value of the dependent variable. However NLS estimation of eq. (4) does not require exclusion of these 16 diseases. We will therefore report NLS estimates of the parameters of eq. (4).

C. Empirical results

I will report NLS estimates of four versions of eq. (4). In the first version, the dependent variable is defined as the total number of drugs, and θ_L and θ_H are both constrained to be equal to one, i.e. I impose the restriction that DALYs in low-mortality and high-mortality developing regions are given the same weight as DALYs in the developed region in the perceived burden of disease. In the second version, the dependent variable is again defined as the total number of drugs, but the restrictions are not imposed; θ_L and θ_H are freely estimated. The third and fourth versions are restricted and unrestricted models in which the dependent variable is defined as the number of priority-review drugs.

The estimates are presented in Table 4. Estimates of the first version are shown in column 1. Consistent with Figure 2b, there is a significant positive log-linear relationship between world DALYs and the total number of drugs. The elasticity (β) is approximately 0.25: a 10% increase in world DALYs is associated with about a 2.5% increase in the

number of drugs. In column 2 we allow DALYs in different regions to have different effects on the number of drugs. The estimates of θ_L and θ_H are both very close to zero, and not nearly statistically significant. This suggests that the number of drugs depends only on DALYs in the developed region, and not at all on DALYs in the other two regions. Relaxing the restrictions that $\theta_L = \theta_H = 1$ has very little effect on the estimated elasticity. A 10% increase in developed-region DALYs is associated with about a 2.1% increase in the number of drugs.

Estimates of restricted and unrestricted models of priority-review drugs are shown in columns 3 and 4. These estimates are very similar to the estimates of the models of the total number of drugs. The estimates in column 4 suggest that the number of priority-review drugs depends only on DALYs in the developed region, and not at all on DALYs in the other two regions. A 10% increase in developed-region DALYs is associated with about a 2.6% increase in the number of priority-review drugs.

II. The relationship between the number of DALYs attributable to a disease and the number of drugs launched to treat the disease in approximately 50 countries

We showed above that the number of drugs to treat a disease sold *in the U.S.* depends only on DALYs in the developed region, and not at all on DALYs in the other two regions. This does not necessarily imply that the number of drugs to treat a disease sold *throughout the world* is unrelated to the burden of disease in developing countries. Now I will re-examine this issue using data on drug launches during 1982-2002 in over 50 developed and developing countries.

The data on drug launches come from the *IMS Drug Launches* database. This database has tracked new product introductions worldwide since 1982. In August 2001 the database contained over 165,000 records of individual product introductions. Seventy-two countries are covered; 52 of them have been tracked since 1982. Data on product introductions is gathered from the IMS Health network of offices around the world and reflects the information on the product at the time of launch into each country. Each record in the database contains the following information: the date and country of product launch, the active ingredient(s) of the product, a dummy variable indicating

whether the product's ingredient is a new chemical entity (i.e. whether no products containing this ingredient have been launched anywhere before), and the therapeutic class of the product.[8]

Twenty-six of the therapeutic classes defined by IMS appear to correspond closely to diseases in WHO's burden of disease classification. I calculated the number of new chemical entities (NCEs) launched in each of these therapeutic classes. The 26 therapeutic classes, number of NCEs launched in the class since 1982, and corresponding WHO disease are shown in Table 5.

Unfortunately, the figures on the number of NCEs launched in at least some of the therapeutic classes appear to be inaccurate. For example, only two NCEs were classified as anti-Alzheimer products (IMS therapeutic class N7D), but according to Mosby, four NCEs used to treat Alzheimer's (donepezil hydrochloride, galantamine hydrobromide, rivastigmine tartrate, and tacrine hydrochloride) have been approved since 1993.[9] Also, only four NCEs were classified as anti-malarials, but as shown in Table 3, 14 drugs for the treatment for malaria are currently on the U.S. market.

Despite the apparent incompleteness of the data, examining the relationship between the number of DALYs from a disease and the number of NCEs launched since 1982 in the IMS therapeutic class corresponding to the disease may be worthwhile. Table 6 shows estimates of eq. (4) based on these data.[10] Since some of these drugs have not been launched in the U.S., they cannot all be classified as either priority-review or standard-review drugs. We therefore analyze just the total number of drugs launched.

In the first column, θ_L and θ_H are both constrained to be equal to one, i.e. I impose the restriction that DALYs in low-mortality and high-mortality developing regions are given the same weight as DALYs in the developed region in the perceived burden of disease. Consistent with our earlier estimates, there is a significant positive log-linear relationship between world DALYs and the number of drugs launched. The elasticity (β) is much larger than it was before: a 10% increase in world DALYs is associated with

[8] The database also contains information on indications; unfortunately, I do not have access to this information.
[9] A possible explanation is that drugs with multiple indications may be listed in only one therapeutic class.
[10] Since no drugs were launched in almost a third of the therapeutic classes, estimation of eq. (4) (which does not require exclusion of observations with zero launches) is particularly appropriate.

about a 13.3% increase in the number of drugs launched. In the second column, the restrictions are not imposed; θ_L and θ_H are freely estimated, i.e. we allow DALYs in different regions to have different effects on the number of drugs launched. The estimates of θ_L and θ_H are not statistically significantly different from zero. Once again, this suggests that the number of drugs depends only on DALYs in the developed region, and not at all on DALYs in the other two regions. Relaxing the restrictions $\theta_L = \theta_H = 1$ causes a substantial increase in the estimate of β. However, since we can't reject the hypothesis that $\theta_L = \theta_H = 0$, in column 3 we exclude LMD and HMD from the equation. The estimate of β is now .53.

The first two analyses suggest that both the number of drugs used to treat a disease and sold in the U.S., and the number of drugs launched in over 50 countries since 1982, depend only on DALYs in the developed region, and not at all on DALYs in the other two regions.

III. The relationship between incidence of a disease and the number of articles published in scientific journals pertaining to drug therapy for that disease

The third and final part of our empirical analysis is an examination of the relationship between incidence of a disease, by region, and the number of articles published in scientific journals pertaining to drug therapy for that disease. The incidence of disease is defined as the number of new cases of disease occurring in a population during a defined time interval. The number is useful to epidemiologists because it is a measure of the risk of disease.[11]

Systematic data on incidence, by region, are not available for most diseases, but reliable data on the incidence of cancer, by cancer site (e.g. breast and prostate) and region (more vs. less deceloped) 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

[11] See http://en.wikipedia.org/wiki/Incidence_(epidemiology). Incidence is not to be confused with *prevalence*, which is defined as the number of individuals with a certain disease in a population at a specified time divided by the number of individuals in the population at that time. This measure differs from incidence in that it does not convey information about risk.

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.

Data on the number of articles published in scientific journals pertaining to drug therapy for each of 25 cancer sites were obtained by searching MEDLINE (Medical Literature Analysis and Retrieval System Online), the U.S. National Library of Medicine's (NLM) 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 4,800 journals published in the United States and more than 70 other countries primarily from 1966 to the present.[12]

References to articles are indexed with terms from NLM'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 Medical Subject Headings 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.

At the highest (most general) level of the MeSH hierarchical structure are the following 15 headings:

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[12] 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 NLM's broad user community are also included. Citations for MEDLINE are created by the NLM, international partners, and collaborating organizations.

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*; our 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.[13]

Table 7 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:

$TOTAL\_CITE_i$	= the total number of MEDLINE articles pertaining to cancer site i
$DRUG\_CITE_i$	= the number of MEDLINE articles pertaining to drug therapy for cancer site i
$NONDRUG\_CITE_i$	= other MEDLINE articles pertaining to cancer site i

[13] Novelty is also a necessary condition for *patenting*. A searchable U.S. patents database exists, and some investigators have used patent counts and citations as innovation indicators. However the U.S. patent classification system is much cruder than the MeSH classification system with respect to medical innovation, and is inadequate for our purposes.

$$= TOTAL\_CITE_i - DRUG\_CITE_i$$

Using the data in Table 7, I estimated the following four models:

Model 1: $\ln DRUG\_CITES_i = \alpha_1 + \beta_{DW} \ln INC\_WORLD_i + e_i$

Model 2: $\ln NONDRUG\_CITES_i = \alpha_2 + \beta_{NW} \ln INC\_WORLD_i + e_i$

Model 3: $\ln DRUG\_CITES_i = \alpha_3 + \beta_{DM} \ln INC\_MORE_i + \beta_{DL} \ln INC\_LESS_i + e_i$

Model 4: $\ln NONDRUG\_CITES_i = \alpha_4 + \beta_{NM} \ln INC\_MORE_i + \beta_{NL} \ln INC\_LESS_i + e_i$

where:

INC_WORLD_i = the incidence of cancer at site i throughout the world
INC_MORE_i = the incidence of cancer at site i in the more developed region
INC_LESS_i = the incidence of cancer at site i in the less developed region

Estimates of these equations are shown in Table 8. 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.

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 ($\beta_{NM} - \beta_{NL} = 0.27$).

Discussion

The first two analyses indicated that both the number of drugs used to treat a disease and sold in the U.S., and the number of drugs launched in over 50 countries since 1982, depend only on DALYs in the developed region, and not at all on DALYs in the other two regions. The third analysis indicated that the number of drug-therapy publications in over 4,800 journals published in more than 70 countries is related to cancer incidence in the more-developed region but not to incidence in the less-developed region. I think that the most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation has been weak or nonexistent incentives for firms to develop medicines for diseases primarily afflicting people in developing countries. Although the size of the developing-region market is large—it accounts for 78% of world population and 85% of world DALYs—the prices manufacturers expect to receive in this market are probably very low.[14, 15] One reason for low expected prices is low per capita income. Other possible reasons are weak intellectual property protection and government drug reimbursement policies.

Pharmaceutical innovation is generally characterized by very high fixed costs and low marginal costs: suppose it costs $800 million to produce and sell the first pill, and $1 to produce and sell the second and subsequent pills. Due to the large size of the developing-region market, the expected price need not exceed marginal cost by very much for the manufacturer to at least break even. If there are 1 billion consumers, the manufacturer would break even if the price per pill were $1.80. (If there were only 100 million consumers, the price per pill would have to be five times as high ($9 per pill) for the manufacturer to break even.) But weak intellectual property protection and

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[14] 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 ($\beta_{NM} - \beta_{NL}$).

[15] Danzon et al found that drug companies were likely to launch drugs earlier in countries with higher expected drug prices, which tend to be countries with higher incomes. (Patricia, Y. Richard Wang, and Liang Wang (2003), "The Impact of Price Regulation on the Launch Delay of New Drugs – A Study of Twenty-Five Major Markets in the 1990s," http://hc.wharton.upenn.edu/danzon/PDFFiles/LaunchDelayPaper.pdf)

government drug reimbursement policies (or price controls) may prevent the firm from charging a price that allows it to earn positive profits, despite the large potential market.

Economic research has demonstrated that investment in R&D is greatly affected by incentives that are offered for R&D. In his influential study of almost a thousand inventions in four different industries, Schmookler (1966) argued that it is the expected profitability of inventive activity that determines the pace and direction of industrial innovation.[16] Empirical economic research in the areas of: (1) energy efficiency; (2) military design competitions; (3) orphan drugs; and (4) health care reform confirm that when incentives are increased or decreased, R&D investment increases or decreases correspondingly.

In response to the enormous increases in energy prices during the 1970s, firms significantly stepped up spending on energy-R&D projects, in a targeted attempt to reduce energy consumption.[17] Studies on defense procurement similarly confirm this principle. Whenever the government offers to award a significant defense contract, potential military contractors make large investments of their own funds in R&D for the types of products the government is seeking to buy.[18]

In 1983, the U.S. Congress passed the Orphan Drug Act (ODA), which gave firms special incentives to develop drugs for diseases afflicting fewer than 200,000 Americans.[19] The ODA contains provisions that reduce the private cost of, and raise the appropriability of private returns to, research on rare diseases. First, for seven years following FDA approval, the FDA cannot approve another drug for the same indication without the sponsor's consent. According to the FDA, this is the "most sought incentive." Second, drug makers qualify for a tax credit for up to 50 percent of clinical testing expense.[20] In addition, the FDA provides grant support for investigation of rare

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[16] Schmookler, Jacob (1966), *Invention and Economic Growth* (Cambridge: Harvard University Press).
[17] Popp, David, "Induced Innovation and Energy Prices," NBER Working Paper No.w8284, May 2001; Lichtenberg, Frank R., "Changing Market Opportunities and the Structure of R&D Investment: The Case of Energy," *Energy Economics* 9(3), July 1987, 154-8; Lichtenberg, Frank R., "Energy Prices and Induced Innovation," *Research Policy* 15, 1986, 67-75.
[18] Lichtenberg, Frank R., "The Private R&D Investment Response to Federal Design and Technical Competitions," *American Economic Review* 78(3), June 1988, 550-9.
[19] See http://www.fda.gov/orphan/oda.htm.
[20] http://www.fda.gov/orphan/taxcred.htm

disease treatments.[21] Together, these provisions increase equilibrium R&D investment by both increasing effective market size and reducing fixed (sunk) costs.

The FDA claims that "the ODA has been very successful",[22] in the sense that it has stimulated the development of many drugs for rare diseases, and the evidence supports this. Figure 3 shows the cumulative number of orphan drugs (drugs that are *currently* designated as orphan drugs) and other drugs approved by the FDA, 1939-2001. The average annual number of orphan drugs approved by the FDA has been 1530% higher since 1983 than it was before 1983. The average annual number of other drugs approved has been only 149% higher since 1983 than it was before 1983.

Both firm-level and industry-level evidence are consistent with the hypothesis that the threat of pharmaceutical price controls in the Clinton administration's 1992-93 health care reform proposals had a significant negative effect on pharmaceutical R&D investment. Economic theory and evidence indicate that, in general, a firm's incentive to invest is positively related to its market value[23] (relative to its replacement costs). In Lichtenberg (2004), I presented firm-level evidence about pharmaceutical R&D investment that is consistent with this: my estimates indicate that a 10% decrease in market value is associated with a 2.25% decrease in R&D expenditure, holding constant tangible assets, past R&D investment, and cash flow.[24] Ellison and Mullin (1997) estimated that the threat of Clinton health care reform reduced the market value of pharmaceutical firms by 44% during the period from September 1992 to October 1993.[25]

We would therefore expect to observe an industry-wide decline in the rate of growth of pharmaceutical R&D investment at the time of (or soon after) the threat of pharmaceutical price controls.[26] As shown in Figure 4, the growth rate of pharmaceutical industry R&D investment was much lower during the period 1993-95 than it was during any other period since 1987.

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[21] http://www.fda.gov/orphan/grants/info.htm
[22] http://www.fda.gov/orphan/
[23] If the stock market is efficient, the value of the firm at time *t* is the expected present discounted value of its future net cash flows, conditional on the information available at time *t*.
[24] Lichtenberg, Frank R., "Public policy and innovation in the U.S. pharmaceutical industry," in *Public Policy and the Economics of Entrepreneurship*, ed. by Douglas Holtz-Eakin and Harvey S. Rosen (MIT Press, 2004), pp. 83-113.
[25] Ellison, Sara Fisher and Mullin, Wallace P., "Gradual Incorporation of Information into Stock Prices: Empirical Strategies," NBER Working Paper No. W6218, October 1997.
[26] Reaction of investment to its determinants is often subject to lags.

The availability of protection for any intellectual property that is developed is a particularly important incentive to R&D investment. As Levin *et al.* note, "to have the incentive to undertake research and development, a firm must be able to appropriate returns sufficient to make the investment worthwhile" (p. 783).

One form of incentive for R&D investment that governments offer is intellectual property protection. The protection of intellectual property is a very important incentive to R&D investment in many industries. Indeed, economic research has found that many inventions would not have been made absent patent protection.[27]

Some economists, such as 1993 Nobel Laureate Douglass North opine that the invention of intellectual property and its protection caused an explosion in creativity that was the basic force behind the Industrial Revolution.[28] As Jones (1998) observes, "sustained economic growth is a very recent phenomenon" — it began with the Industrial Revolution in Britain in the 1760s — and "the thesis of Douglass North and a number of other economic historians is that the development of intellectual property rights, a cumulative process that occurred over centuries, is responsible for modern economic growth"[29] (p. 81). "…[H]istory suggests that it is only when the *market* incentives were sufficient that widespread innovation and growth took hold" (p. 83).

Stern *et al.* present evidence that countries that offer greater patent protection at home have more patents in the U.S. than countries with less patent protection.[30] Hall and Jones (1998) found that "A country's long-run economic performance is determined primarily by the institutions and government policies that make up the economic environment within which individuals and firms make investments, create and transfer ideas, and produce goods and services."

In the long run, even imitators (such as generic drug companies) can benefit from stronger intellectual property protection. Imitators survive by copying innovators' inventions. If invention declines (*e.g.*, due to weakening of IP protection), there is less

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[27] E. Mansfield, "Patents and Innovation: An Empirical Study," Management Science, 31, 1986.
[28] Hall, Robert E. and Charles I. Jones, "Why Do Some Countries Produce So Much More Output per Worker than Others?" March 11, 1998.
[29] Jones, Charles (1998), *Introduction to Economic Growth* (New York: Norton).
[30] Stern, Scott, Michael E. Porter, and Jeffrey L. Furman, "The Determinants of National Innovative Capacity", NBER Working Paper No. 7876, September 2000. Stern, *et al.* find that a one standard-deviation increase in a country's intellectual property score is associated with a 22 percent increase in the number of U.S. patents it has.

for imitators to copy. Weaker IP protection makes it easier for imitators to dip into the pool of innovations, but it also shrinks the size of that pool; the latter effect may dominate the former.[31]

All of this evidence suggests that, across industries, a high average level of intellectual property protection may be economically beneficial. Moreover, patent protection may be especially important for pharmaceutical R&D.

As Levin *et al.*(1987) argue, in principle, there are several ways in which a firm can "protect the competitive advantages of new and improved processes and products," including patents, secrecy, lead time, moving quickly down the learning curve, and sales or service efforts.[32] They surveyed high-level R&D executives in more than one hundred manufacturing industries to determine the effectiveness of these alternative mechanisms for protecting intellectual property. They found that "generally, lead time, learning curves, and sales and service efforts were regarded as substantially more effective than patents in protecting products" (p.795). "*In only one industry, drugs, were product patents regarded by a majority of respondents as strictly more effective than other means of appropriation*" (p. 796, emphasis added).[33]

Congress has recognized the importance of patent protection as an incentive to pharmaceutical R&D. For example, as part of the Hatch-Waxman Act, Congress provided for patent term extensions to offset some of the time that drugs spend in clinical testing and in the FDA review process.

Mansfield (1986, p. 175) provided estimates of the percentage of inventions that would not have been commercially introduced if patent protection could not have been obtained, by industry, for twelve industries during the period 1981-83. Mansfield found that 65% of pharmaceutical inventions would not have been introduced if patent protection could not have been obtained; for the eleven other industries he studied, the

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[31] Imitators always favor weaker protection for innovations that have already been produced, but may benefit from stronger protection for innovations yet to be produced.

[32] Levin, C.T., Klevorick, A.K., Nelson, R.R., & Winter, S.G. 1987, "Appropriating the Returns From Industrial R&D," *Brookings Papers on Economic Activity*, 3: pp. 783-820.

[33] They argued that "the most probable explanation for the robust finding that patents are particularly effective in chemical industries [including pharmaceuticals] is that comparatively clear standards can be applied to assess a chemical patent's validity and to defend against infringement" (p. 798), whereas such standards cannot be applied to assess other kinds of patents (e.g. patents on components of complex systems).

(unweighted) average percentage of inventions that would not have been introduced was only 8%.

The typical expenditures in R&D for a new drug are very large. According to a 1993 Congressional Office of Technology Assessment report, the average after-tax cost of R&D cash outlays for each new drug that reached the market in the 1980's was approximately $194 million in 1990 dollars or $265 million in current 2001 dollars.[34] R&D costs for new drugs have increased significantly since the 1980's.[35] 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.[36] The drug development process is highly risky and time consuming, as only five in 5000 compounds that enter pre-clinical testing make it to human testing, and only one out of these five compounds is approved by the FDA. In addition, it takes an average of twelve to fifteen years from the time that a potential drug is discovered until it receives FDA approval. Innovator drug companies that obtain patents on their products face intense competition both prior to and after the expiration of the applicable drug patents. Pharmaceutical companies carefully consider the large risks and potential rewards from their R&D into new drugs.[37]

Firms invest in R&D in the expectation that they will earn sufficient profits to recover their R&D costs and earn an economic profit for their shareholders if the R&D leads to a commercially successful product. According to estimates of PhRMA, however, on average only 3 out of every 10 prescription drugs generate revenues that equal or exceed average R&D costs.[38] Innovating pharmaceutical firms will not find it

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[34] Office of Technology Assessment, "Pharmaceutical R&D: Costs, Risks, and Rewards," Washington, US GPO, 1993.

[35] *See* PhRMA, Monthly Report, March 2001, on the website http://www.phrma.org. The estimates are based on J. DiMasi, "Risks, Regulation, and Rewards in New Drug Development in the U.S.," Regulatory Toxicology and Pharmacology, Vol. 19, No. 2, 1994 (228-235).

[36] http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=29

[37] For a description of how Merck, one of the largest US-based pharmaceutical companies, evaluates risk in R&D, *see* N.A. Nicols, "Scientific Management at Merck: An Interview with CFO Judy Lewent," Harvard Business Review, Jan. 1994. There is also evidence that the National Institutes of Health considers economic benefits and costs when allocating its enormous biomedical research budget. *See* Lichtenberg, Frank, "The Allocation of Publicly-Funded Biomedical Research," in *Medical Care Output and Productivity*, ed. by Ernst Berndt and David Cutler (University of Chicago Press, 2001).

[38] "Why Do Medicines Cost So Much?," http://www.phrma.org/publications/brochure/questions /whycostmuch.phtm. The finding is based on H. Grabowski and J. Vernon, "Returns to R&D on New Drug Introductions in the 1980s," *Journal of Health Economics*, Vol. 13, 1994.

economically worthwhile to undertake the risk of investing in the development of a new drug where less than 1/3 of new drugs earn back their costs of R&D if the new drug can be easily copied. Imitator firms will target the 1/3 of new drugs that are successful and decrease the expected profits of the innovators. By decreasing the expected revenues and profits for these successful new drugs, they will decrease the economic incentive of pharmaceutical companies to undertake the risky R&D that is involved in inventing and getting approval of a new drug.

Conclusion

Longevity has increased throughout the world during the last half century. According to the United Nations, life expectancy at birth increased from 46.5 years in 1950-55 to 65.0 years in 1995-2000. The rate of increase in the last quarter of the 20th century was only half as great as the rate of increase in the previous quarter; still, life expectancy at birth increased 5.2 years from 1975-1980 to 1995-2000. Moreover, longevity in less-developed regions has grown much more rapidly than longevity in more developed regions (Figure 5). In the last two decades, the gap has narrowed by 3.5 years. Unlike per capita income, longevity is converging.

Nevertheless, at the end of the last century, life expectancy at birth in the developing region was 12 years lower than life expectancy at birth in the developed region. In a previous paper, I found that, although new drug launches account for a significant fraction (as high as 40%) of global longevity increase, cross-country variation in the number of NCE launches explains very little of the international variation in longevity levels. However, that paper examined the effect of variation in access to drugs that have been developed. If new drugs that *might have been*, but were not, developed (e.g. due to lack of incentives) were also somehow taken into account, then pharmaceutical innovation might account for a nontrivial, and perhaps a significant, fraction of international variation in longevity levels.

Three different analyses of the relationship between pharmaceutical innovation and the burden of disease indicated that the amount of pharmaceutical innovation is positively related to the burden of disease in developed countries but not to the burden of

disease in developing countries. The amount of other medical innovation also appears to be positively related to the burden of disease in developed countries but not to the burden of disease in developing countries, although the developed-vs.-developing difference is smaller than in the case of pharmaceutical innovation.

I think that the most plausible explanation for the lack of a relationship between the burden of disease in developing countries and the amount of pharmaceutical innovation is that incentives for firms to develop medicines for diseases primarily afflicting people in developing countries have been weak or nonexistent. Economic research has demonstrated that investment in R&D is greatly affected by incentives that are offered for R&D. To increase the rate of development of drugs for diseases primarily afflicting people in developing countries, incentives for developing these drugs must be strengthened.

The establishment of purchase commitment funds, as proposed by Michael Kremer (2000), may be the most efficient way to stimulate the development and production of these drugs.[39] Kremer argues that government-directed research programs may be well-suited for basic research, but for the later, more applied stages of research, committing to compensate successful private drug developers has important advantages. Under such programs, the public pays only if a successful drug is actually developed. This gives pharmaceutical firms and scientists strong incentives to self-select research projects that have a reasonable chance of leading to a drug, and to focus on developing a viable drug rather than pursuing other goals. Committing to purchase drugs and make them available to poor countries may be attractive relative to other ways of rewarding drug developers. Extending patents on other pharmaceuticals to reward developers of new drugs would place the entire burden of financing vaccines on those needing these other pharmaceuticals. Increasing prices for current drugs without explicit incentives for development of new drugs would be insufficient to spur new research.

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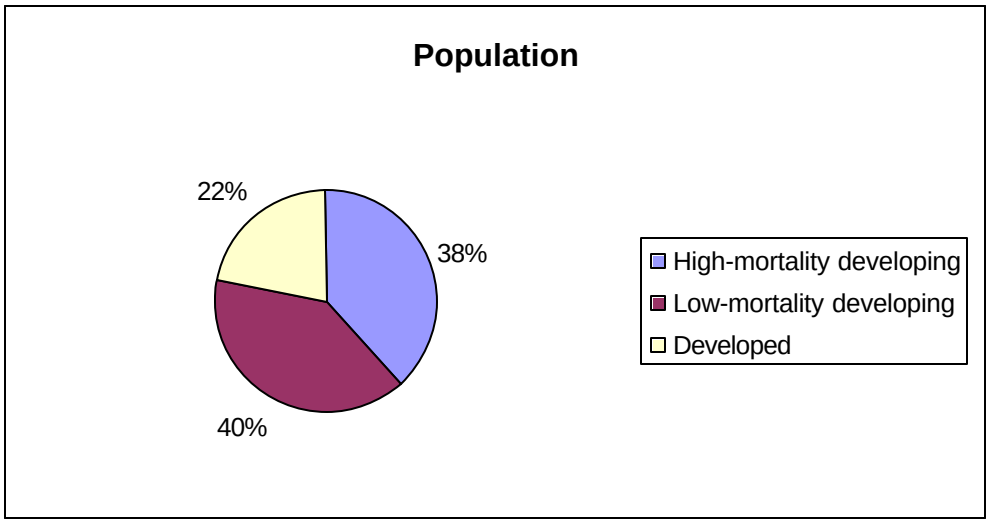
[39] Kremer's proposal pertained to vaccines, but it could also be applied to pharmaceuticals. See Kremer, Michael, "Creating Markets for New Vaccines, Part I: Rationale," NBER Working Paper No. 7716, May 2000, and "Creating Markets for New Vaccines, Part II: Design Issues," NBER Working Paper No. 7717, May 2000.

Figure 1
Regional distributions of population and disease burden



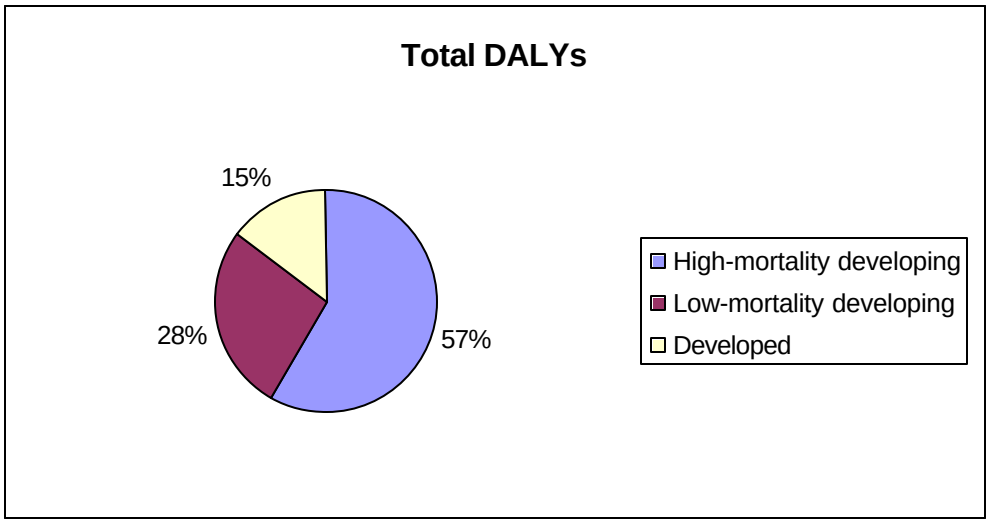


Figure 2a
Relationship between World DALYs and Number of drugs

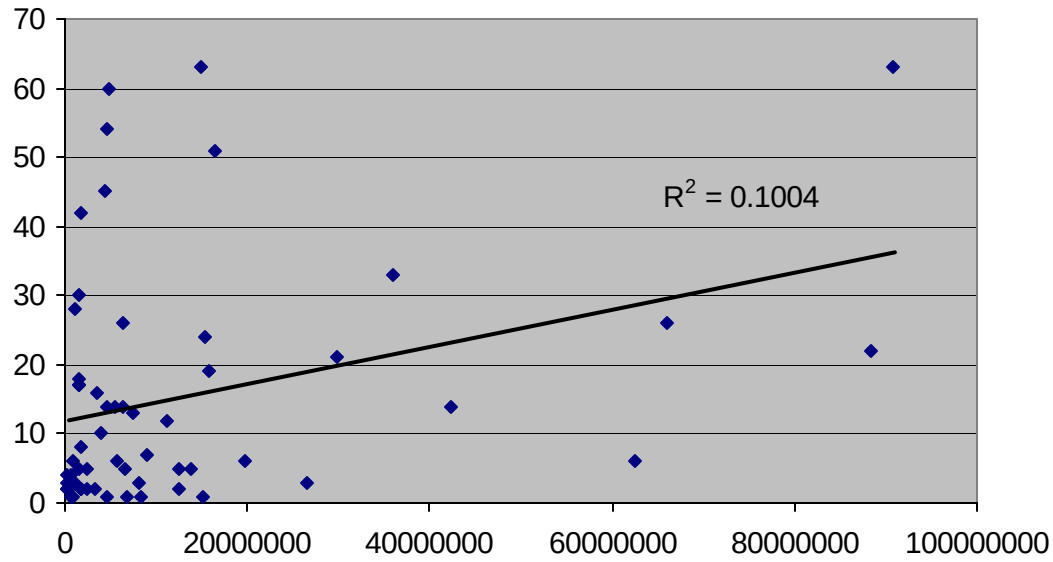


Figure 2b
Relationship between log(World DALYs) and log(Number of drugs)

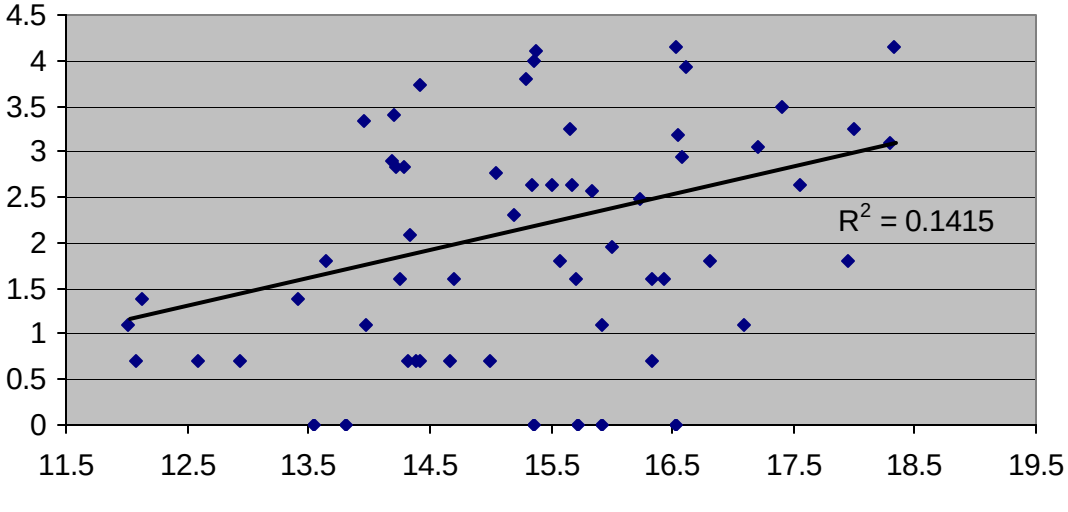


Figure 3
Cumulative number of orphan drugs and other drugs approved by the FDA, 1939-2001

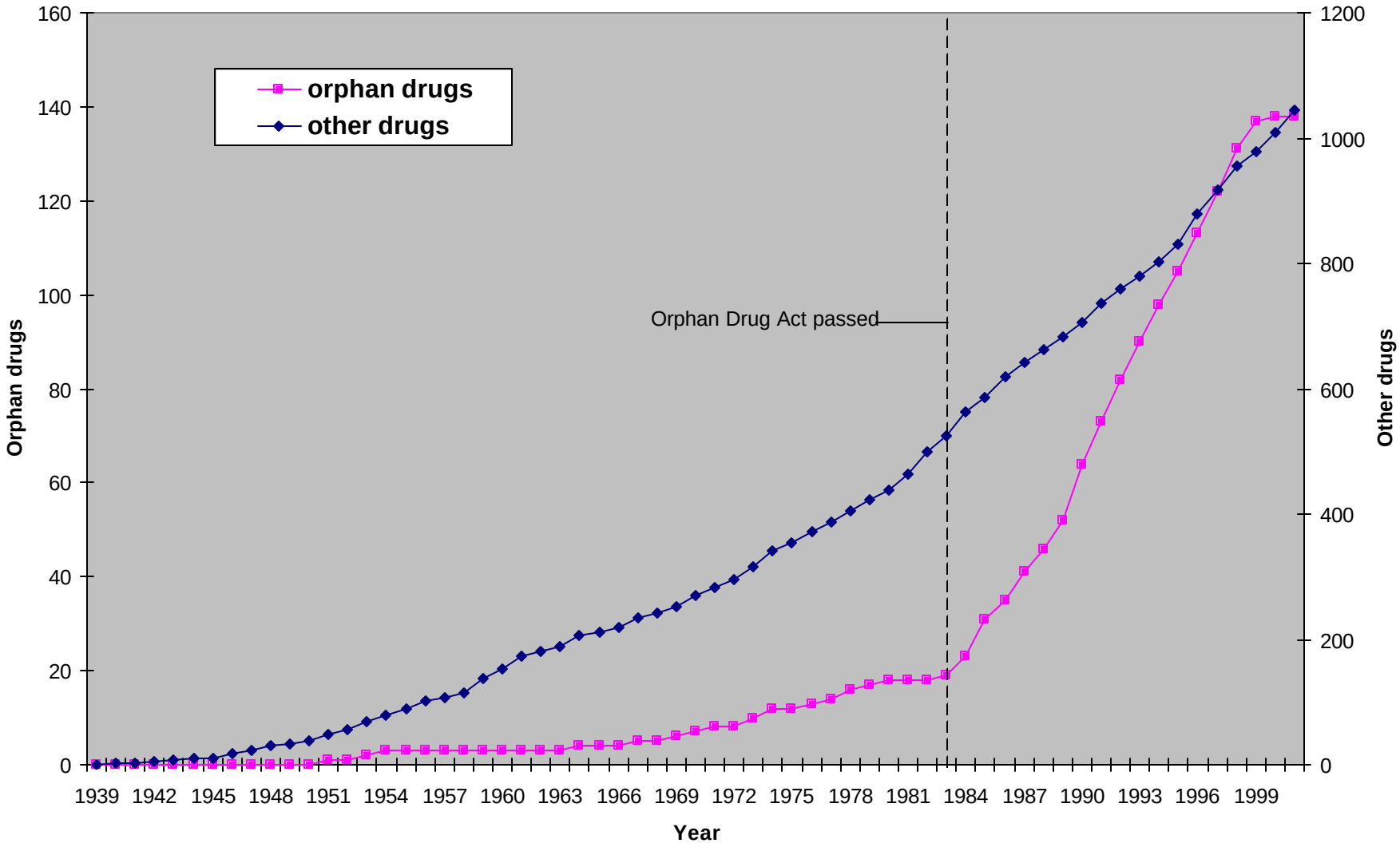


Figure 4
Annual % change in Pharmaceutical R&D, 1987-2000

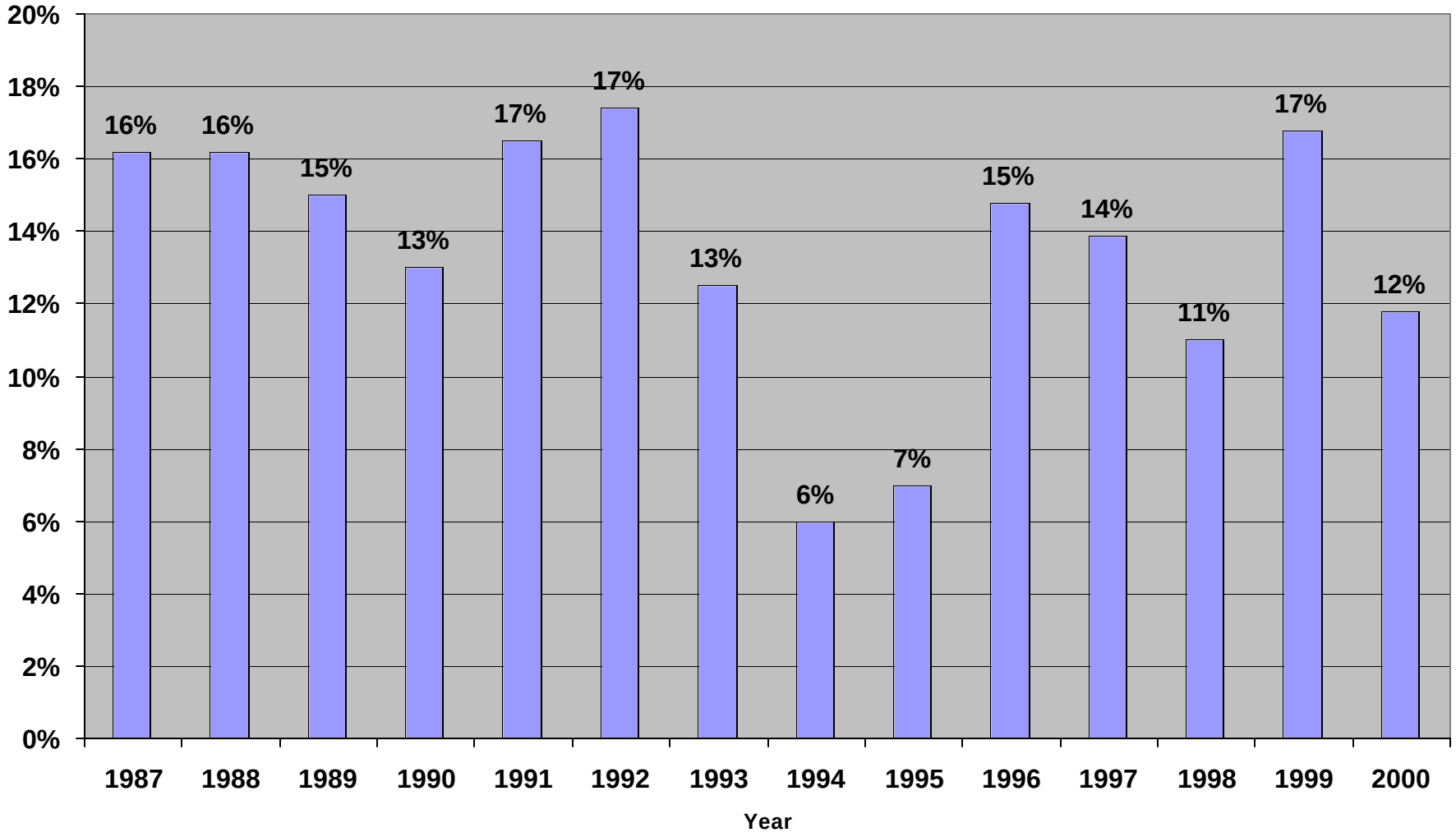


Figure 5
Life expectancy at birth, both sexes, by region

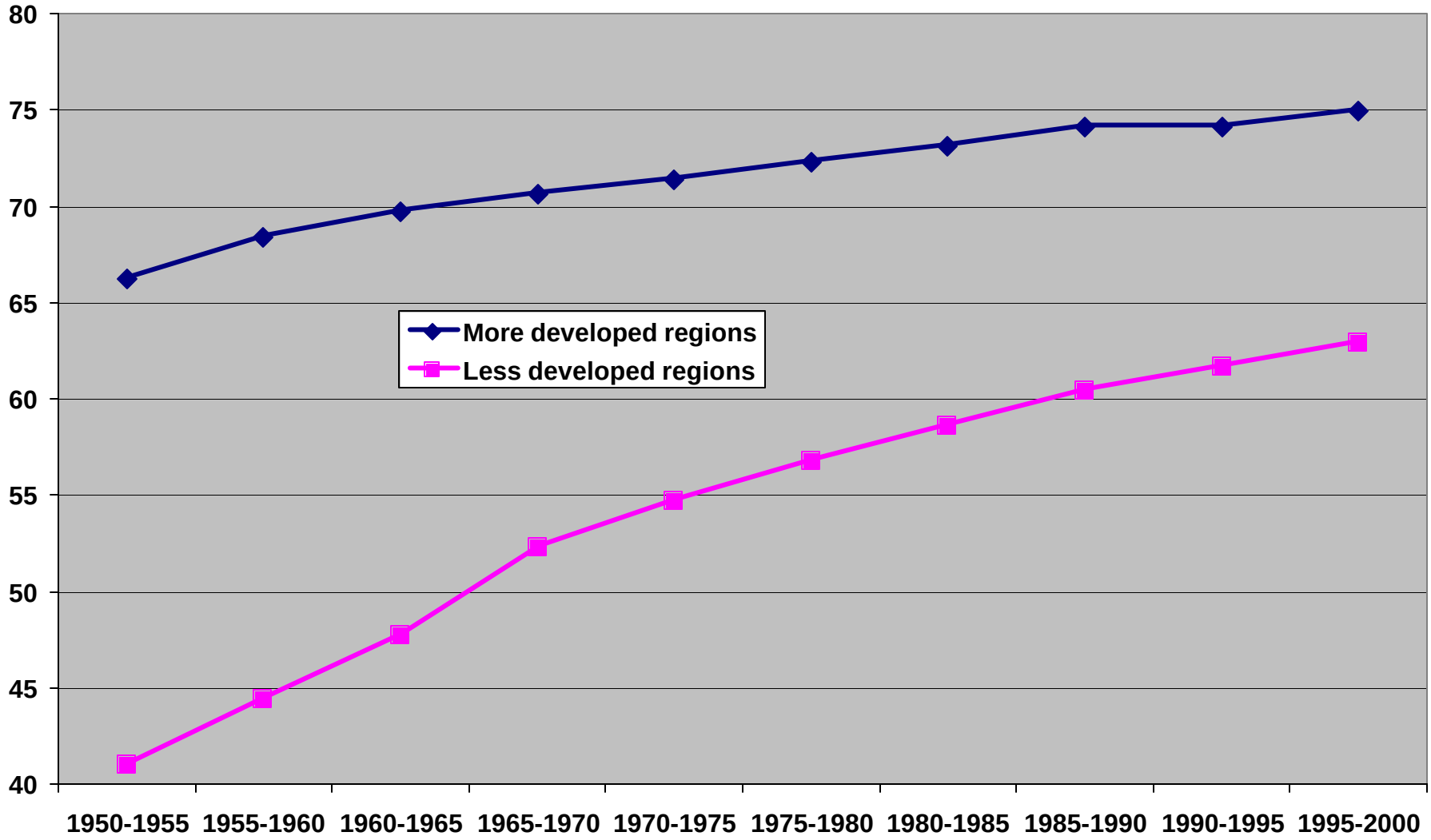


Table 1
Who diseases and Mosby indications of use

WHO burden of disease cause	Mosby indication(s)
Tuberculosis	Tuberculosis; Tuberculosis, disseminated; Tuberculosis, fulminating; Tuberculosis, immunization; Tuberculosis, meningitis
Syphilis	Syphilis; Syphilis, congenital
HIV/AIDS	Human immunodeficiency virus infection
Diarrhoeal diseases	Diarrhea
Pertussis	Pertussis
Poliomyelitis	Poliomyelitis, immunization
Diphtheria	Diphtheria; Diphtheria, immunization
Measles	Measles, immunization
Tetanus	Tetanus; Tetanus, immunization
Meningitis	Meningitis
Hepatitis B	Hepatitis B; Hepatitis B, immunization; Hepatitis B, Post-Exposure prophylaxis
Hepatitis C	Hepatitis C
Malaria	Malaria; Malaria, prophylaxis
Schistosomiasis	Schistosomiasis
Leishmaniasis	Leishmaniasis
Onchocerciasis	Onchocerciasis
Leprosy	Leprosy
Japanese encephalitis	Japanese encephalitis, immunization
Trachoma	Trachoma; Trachoma, adjunct
Intestinal nematode infections	Onchocerciasis; Strongyloidiasis of the intestinal tract
Ascariasis	Ascariasis
Trichuriasis	Trichuriasis
Hookworm disease	Hookworm
Lower respiratory infections	Lower respiratory tract infection
Upper respiratory infections	Upper respiratory tract infection
Otitis media	Otitis media; Otitis media, adjunct
Stomach cancer	Stomach cancer
Colon/rectum cancer	Colorectal cancer; Colorectal cancer, adjunct
Trachea/bronchus/lung cancers	Cancer, lung
Melanoma and other skin cancers	Melanoma, malignant
Breast cancer	Cancer, breast
Prostate cancer	Prostatic cancer
Bladder cancer	Bladder cancer
Lymphomas, multiple myeloma	Lymphoma; Lymphoma, adjunct; Lymphoma, Burkitt's; Lymphoma, follicular; Lymphoma, histiocytic; Lymphoma, Hodgkin's; Lymphoma, lymphocytic; Lymphoma, non-Hodgkin's; Lymphoma, palliation; Lymphoma, skin manifestations; Lymphoma, T cell, cutaneous; Lymphosarcoma; Myeloma, multiple

Leukaemia	Leukemia; Leukemia, acute; Leukemia, acute erythroid; Leukemia, acute lymphoblastic; Leukemia, acute monocytic; Leukemia, acute myeloblastic; Leukemia, acute myelogenous; Leukemia, acute myelogenous, adjunct; Leukemia, acute myeloid; Leukemia, acute nonlymphocytic; Leukemia, acute promyelocytic; Leukemia, adjunct; Leukemia, central nervous system; Leukemia, chronic granulocytic; Leukemia, chronic lymphocytic; Leukemia, chronic myelogenous; Leukemia, hairy cell; Leukemia, meningeal; Leukemia, nonlymphocytic; Leukemia, monocytic; Leukemia, palliation
Diabetes mellitus	Diabetes mellitus
Unipolar depressive disorders	Depression
Bipolar affective disorder	Bipolar affective disorder
Schizophrenia	Schizophrenia
Epilepsy	Epilepsy, absence; Epilepsy, petit mal
Alcohol use disorders	Alcohol withdrawal; Alcohol, dependence
Alzheimer and other dementias	Alzheimer's disease; Dementia
Parkinson disease	Parkinson's disease; Parkinson's disease, adjunct
Multiple sclerosis	Multiple sclerosis; Multiple sclerosis, adjunct
Post-traumatic stress disorder	Posttraumatic stress disorder
Panic disorder	Panic disorder
Insomnia (primary)	Insomnia
Migraine	Migraine headache; Migraine headache prophylaxis
Glaucoma	Glaucoma, angle-closure; Glaucoma, angle-closure, adjunct; Glaucoma, open-angle; Glaucoma, open-angle, adjunct; Glaucoma, secondary; Glaucoma, secondary, adjunct
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
Asthma	Asthma
Peptic ulcer disease	Ulcer, peptic; Ulcer, peptic, adjunct
Cirrhosis of the liver	Cirrhosis
Appendicitis	Appendicitis
Nephritis/nephrosis	Nephrosis
Benign prostatic hypertrophy	Prostate, benign hyperplasia
Rheumatoid arthritis	Rheumatoid arthritis
Osteoarthritis	Osteoarthritis; Osteoarthritis, post-traumatic
Periodontal disease	Periodontitis

Table 2

New Drug Applications Approved in Calendar Years 1990-2003 by Therapeutic Potential and Chemical Types

Chemical Type	Priority Review	Standard Review	Total
1 - New molecular entity	166	234	400
2 - New ester, new salt, or other noncovalent derivative	5	26	31
3 - New formulation	82	465	547
4 - New combination	5	68	73
5 - New manufacturer	6	100	106
6 - New indication (Beginning in 1994, Type 6's were tracked as efficacy supplements, not as NDAs.)	0	7	7
7 - Drug already marketed, but without an approved NDA	0	7	7
Total	264	907	1171

*Priority Review: "Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease."

**Standard Review: "The drug appears to have therapeutic qualities similar to those of one or more already marketed drugs."

http://www.fda.gov/cder/rdmt/pstable.htm

Table 3
Burden of disease and number of drugs, by WHO condition

	DALYs				Number of drugs	
WHO condition	World	High-mortality developing	Low-mortality developing	Developed	Total	Priority review
Alcohol use disorders	19843080	2960290	9476544	7406245	6	3
Alzheimer and other dementias	12436576	2751768	3110311	6574496	5	2
Appendicitis	417629	188020	164568	65041	2	0
Ascariasis	1181297	345901	824417	10979	3	2
Asthma	15009578	7154202	5338736	2516640	63	14
Benign prostatic hypertrophy	2427630	956378	1073267	397985	5	1
Bipolar affective disorder	13708452	5619291	5792081	2297080	5	1
Bladder cancer	1548473	628561	302931	616981	5	2
Breast cancer	6317372	1718284	1928703	2670385	26	9
Chronic obstructive pulmonary disease	29917307	8468799	15803052	5645456	21	5
Cirrhosis of the liver	15050712	6567553	5165854	3317304	1	0
Colon/rectum cancer	5762353	863373	2056476	2842504	6	6
Diabetes mellitus	15446371	5293295	6097185	4055891	24	8
Diarrhoeal diseases	62450782	53706104	7767180	977499	6	0
Diphtheria	184726	166243	15876	2607	4	0
Epilepsy	6787179	3649431	2271543	866205	1	0
Glaucoma	1152200	538430	407884	205885	28	10
HIV/AIDS	88429222	82056499	4991768	1380955	22	18
Hepatitis B	1683585	924133	627585	131867	8	2
Hepatitis C	844025	410579	266007	167438	6	1
Hookworm disease	1825121	1243097	576054	5970	2	2
Insomnia (primary)	3405755	1340164	1050559	1015033	16	2
Intestinal nematode infections	4705926	2058460	2622697	24769	1	1
Japanese encephalitis	767165	402746	364108	311	1	0
Leishmaniasis	2356609	2245450	104677	6482	2	0
Leprosy	176583	133186	42719	678	2	2
Leukaemia	4659523	1554457	2040358	1064708	54	31
Lower respiratory infections	90748015	70066664	16534813	4146538	63	14
Lymphomas, multiple myeloma	4359744	2165551	962960	1231233	45	22
Malaria	42279607	41360781	898028	20799	14	7
Measles	26495237	23934177	2330069	230991	3	0
Melanoma and other skin cancers	670687	153064	118206	399417	4	1
Meningitis	6419546	4279166	1638252	502127	14	5
Migraine	7564568	2667932	3008290	1888346	13	3
Multiple sclerosis	1442238	452457	544519	445262	18	6
Nephritis/nephrosis	8236426	4210041	3002114	1024272	1	0
Onchocerciasis	986716	985752	965	0	1	1
Osteoarthritis	16371764	4480390	6568796	5322578	51	15
Otitis media	1473749	776365	550546	146839	30	7
Panic disorder	6636226	2719033	2717534	1199659	5	2
Parkinson disease	1598912	438760	391742	768410	17	8
Peptic ulcer disease	4585012	2326779	1665239	592994	14	0

Periodontal disease	295526	149964	86437	59126	2	0
Pertussis	12464444	11426724	805455	232265	2	0
Poliomyelitis	163779	85341	67045	11393	3	0
Post-traumatic stress disorder	3266208	1231925	1310047	724235	2	0
Prostate cancer	1495234	458266	265306	771662	17	3
Rheumatoid arthritis	4757257	1423592	1813974	1519691	60	19
Schistosomiasis	1759558	1604659	152969	1931	2	2
Schizophrenia	15890710	6457139	7074681	2358890	19	5
Stomach cancer	8149413	1238805	4902889	2007719	3	2
Syphilis	5399909	5139801	240746	19361	14	0
Tetanus	8959660	8192147	763341	4172	7	0
Trachea/bronchus/lung cancers	11258174	1810132	4304895	5143146	12	10
Trachoma	3997477	2057318	1938580	1579	10	2
Trichuriasis	1648752	439114	1202579	7059	2	2
Tuberculosis	36040284	24571204	9728780	1740300	33	11
Unipolar depressive disorders	65910615	26005838	24457124	15447653	26	8
Upper respiratory infections	1815221	1015456	648081	151684	42	4

Table 4
Nonlinear least-squares estimates of the parameters of eq. (4),

$$T_i = \exp(a)\,[DEV_i + q_L\,LMD_i + q_H\,HMD_i]^b$$

based on data in Table 3

column	1	2	3	4
dep. var.	all drugs	all drugs	priority-review drugs	priority-review drugs
β				
estimate	0.2494	0.2113	0.276	0.2568
approx. std. err.	0.0962	0.096	0.1128	0.1226
lower 95%	0.0568	0.0189	0.0501	0.0111
upper 95%	0.4419	0.4036	0.502	0.5024
θ_L				
estimate	1	-0.00112	1	-0.00714
approx. std. err.		0.0195		0.0366
lower 95%		-0.0402		-0.0805
upper 95%		0.038		0.0663
θ_H				
estimate	1	0.00152	1	0.00944
approx. std. err.		0.0111		0.0328
lower 95%		-0.0207		-0.0562
upper 95%		0.0238		0.0751
α				
estimate	-1.1887	-0.0685	-2.7461	-1.8495
approx. std. err.	1.579	1.3958	1.8637	1.8144
lower 95%	-4.3507	-2.8657	-6.4782	-5.4857
upper 95%	1.9732	2.7287	0.9859	1.7866

N = 59.

Table 5
Number of NCEs launched in 26 therapeutic classes since 1982

Number of NCEs launched since 1982	IMS therapeutic class code	IMS therapeutic class name	Corresponding WHO Disease
55	L	Cytostatics	Malignant neoplasms
25	J5C	HIV ANTIVIRALS	HIV/AIDS
24	R3	BRONCHODILATORS AND ANTI-ASTHMA PREPARATIONS	Asthma
20	N6A	ANTIDEPRESSANTS	Unipolar depressive disorders
18	C2	ANTIHYPERTENSIVES	Hypertensive heart disease
16	A10	DRUGS USED IN DIABETES	Diabetes mellitus
16	A2B	ANTIULCERANTS	Peptic ulcer disease
12	N3	ANTI-EPILEPTICS	Epilepsy
10	N4	ANTI-PARKINSON DRUGS	Parkinson disease
8	N2C	ANTI-MIGRAINE PREPARATIONS	Migraine
7	C4	CEREBRAL AND PERIPHERAL VASOTHERAPEUTICS	Cerebrovascular disease
6	A7	ANTIDIARRHOEALS, ORAL ELECTROLYTE REPLACERS AND INTESTINAL ANTI-INFLAMMATORIES	Diarrhoeal diseases
5	S1E	MIOTICS AND ANTIGLAUCOMA PREPARATIONS	Glaucoma
4	P1D	ANTI-MALARIALS	Malaria
2	J4A	DRUGS FOR THE TREATMENT OF TUBERCULOSIS	Tuberculosis
2	N7D	ANTI-ALZHEIMER PRODUCTS	Alzheimer and other dementias
1	J6A5	Diphtheria sera	Diphtheria
1	J6A4	Tetanus sera	Tetanus
0	J6G2	Pertussis immunoglobulin	Pertussis
0	J6H2	Measles immunoglobulin	Measles
0	J6H4	Hepatitis immunoglobulin	Hepatitis B
0	J6H4	Hepatitis immunoglobulin	Hepatitis C
0	P1C	SCHISTOSOMICIDES	Schistosomiasis
0	J4B	DRUGS FOR THE TREATMENT OF LEPRA	Leprosy
0	S1N	PREPARATIONS TO PREVENT CATARACT AND ANTICATARACTOGENICS	Cataracts
0	S2	OTOLOGICALS	Hearing loss, adult onset

Table 6

Nonlinear least-squares estimates of the parameters of eq. (4),

$$T_i = \exp(a)\,[DEV_i + q_L\,LMD_i + q_H\,HMD_i]^b$$

based on data in Table 5

column	1	2	3
$\underline{\beta}$			
estimate	1.333	2.148	0.528
approx. std. err.	0.551	0.902	0.147
lower 95%	0.196	0.277	0.224
upper 95%	2.471	4.019	0.831
$\underline{\theta_L}$			
estimate	1.000	-0.273	0.000
approx. std. err.		0.356	
lower 95%		-1.011	
upper 95%		0.466	
$\underline{\theta_H}$			
estimate	1.000	0.178	0.000
approx. std. err.		0.113	
lower 95%		-0.056	
upper 95%		0.412	
$\underline{\alpha}$			
estimate	-20.921	-32.248	-5.450
approx. std. err.	9.935	16.128	2.378
lower 95%	-41.425	-65.696	-10.358
upper 95%	-0.416	1.200	-0.542

N = 26.

Table 7

Incidence in 2002, by region, and number of MEDLINE article citations, for 25 cancer sites as defined in GLOBOCAN

Cancer site	ICD10 codes	total number of MEDLINE articles pertaining to cancer site	number of MEDLINE articles pertaining to drug therapy for cancer site	incidence of cancer at site in the less developed region	incidence of cancer at site in the more developed region
Leukaemia	C91-C95	138,971	30,529	175,898	124,202
Lung	C33-C34	98,796	14,341	672,221	676,681
Non-Hodgkin lymphoma	C82-C85,C96	52,485	9,064	149,191	151,096
Colon and rectum	C18-C21	80,738	8,744	355,701	665,731
Ovary etc.	C56,C57.0-4	38,142	7,636	107,541	96,769
Brain, nervous system	C70-C72	106,896	7,435	114,630	74,549
Prostate	C61	44,355	7,015	165,347	513,464
Liver	C22	77,313	6,464	513,060	110,404
Melanoma of skin	C43	46,321	5,039	29,352	130,815
Hodgkin lymphoma	C81	22,973	4,628	34,264	28,033
Stomach	C16	44,298	4,035	619,235	311,154
Bladder	C67	28,574	3,711	130,971	225,242
Multiple myeloma	C90	18,421	3,332	30,473	55,166
Testis	C62	15,731	2,723	20,489	28,103
Pancreas	C25	31,104	2,706	96,650	135,204
Cervix uteri	C53	35,812	2,072	409,404	83,437
Oesophagus	C15	22,324	1,857	386,435	73,875
Oral cavity	C00-C08	36,013	1,683	183,033	91,141
Thyroid	C73	24,347	895	81,656	59,199
Larynx	C32	16,362	694	94,589	64,537
Nasopharynx	C11	7,576	632	72,612	7,189
Other pharynx	C09-C10,C12-C14	4,228	364	81,811	48,459
Breast	C50	118,088	18,959	514,072	636,128
Corpus uteri	C54	27,756	2,891	62,312	136,329
Kidney etc.	C64-C66,C68	38,660	2,848	68,394	139,871

Table 8

Estimates of the relationship between cancer incidence and the number of drug and non-drug MEDLINE citations

Model	1	2	3	4
dep. Var.	ln $DRUG\_CITES_i$	ln $NONDRUG\_CITES_i$	ln $DRUG\_CITES_i$	ln $NONDRUG\_CITES_i$
ln INC_WORLD_i	0.597	0.598		
std. err.	0.210	0.138		
t-stat	2.850	4.330		
p-value	0.009	0.000		
ln INC_MORE_i			0.670	0.433
std. err.			0.209	0.145
t-stat			3.200	3.000
p-value			0.004	0.007
ln INC_LESS_i			-0.065	0.167
std. err.			0.222	0.154
t-stat			-0.290	1.090
p-value			0.774	0.289