EXHIBIT
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Pharmaceutical knowledge-capital accumulation and longevity

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For presentation at the
Conference on Research on Income and Wealth/
National Bureau of Economic Research conference on
Measuring Capital in a New Economy
Federal Reserve Board, Washington, DC,
April 26-27, 2002

Revised October 2002

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Abstract

People value leisure time as well as goods, so longevity increase is an important part of economic growth, broadly defined. R&D is the principal source of economic growth, and the pharmaceutical industry is the most R&D-intensive sector of the economy. In this paper we assess the contribution of pharmaceutical R&D to longevity increase (hence to economic growth), by analyzing the relationship between FDA approvals of new molecular entities and changes in the age distribution of deaths, using longitudinal disease-level data.

We compute the stock of drugs available (i.e., previously approved by the FDA) to treat a given condition in a given year by combining FDA data with data from First DataBank's National Drug Data File. We use the CDC's Compressed Mortality File to measure changes in the age distribution of deaths, by cause of death.

The estimates indicate that approval of standard-review drugs—drugs whose therapeutic qualities the FDA considers to be similar to those of already marketed drugs—has no effect on longevity, but that approval of priority-review drugs—those considered by the FDA to offer significant improvements in the treatment, diagnosis, or prevention of a disease—has a significant positive impact on longevity. Increases in the stock of (labeled and unlabeled) drugs to treat a condition increase the mean age at which people die from that condition, and reduce the probability of dying before the age of 65.

The increase in the stock of priority-review drugs is estimated to have increased mean age at death by 0.39 years (4.7 months) during the period 1979-1998. Ten percent of the total increase in mean age at death was due to the increase in the stock of priority-review drugs. The rate of return on investment in pharmaceutical R&D is 18%. This rate of return reflects only the value of increased longevity among Americans; foreigners also benefit, and evidence suggests that there may be additional benefits of new drugs to Americans, including reduced hospital expenditure and reduced limitations on work and other activities.

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People value leisure time as well as goods, so longevity increase is an important part of economic growth, broadly defined. R&D is the principal source of economic growth, and the pharmaceutical industry is the most R&D-intensive sector of the economy. In this paper we assess the contribution of pharmaceutical R&D to longevity increase (hence to economic growth), by analyzing the relationship between FDA approvals of new molecular entities and changes in the age distribution of deaths, using longitudinal disease-level data.

Until the middle of the twentieth century, analyses of long-run macroeconomic performance were based on an aggregate production function of the form:

$$Y = F(K, N) \qquad (1)$$

where

Y = real GDP (the market value of goods and services produced)
K = capital input
N = labor input

Capital is, of course, a produced means of production, which accumulates according to the perpetual inventory equation $K_{t+1} = (1 - \delta) K_t + I_t$, where δ is the depreciation rate and I denotes investment.

In the last 50 or 60 years, economists have recognized the inadequacies of this production function—its failure to account for important aspects of observed macroeconomic behavior—and have modified and extended it in several ways. The most important modifications have been expansions of the sets of both inputs and outputs accounted for.

By the 1950s, economists realized that most of the growth in output could not be accounted for by growth in capital and labor. Most output growth was due to total factor productivity (TFP) growth—growth in output per unit of total input—which is not accounted for in eq. (1). Growth in TFP was hypothesized to be due to technological

progress. The production function could easily be modified to allow for the existence of technological progress:

$$Y = A\ F(K, N) \qquad (2)$$

where

A = an index of the level of technology.

Solow (1956) demonstrated that in the long run, the growth rate of per capita output would be equal to the rate of technological progress (the growth rate of A). In that paper, Solow assumed that technological progress was exogenous: it descends upon the economy like "manna from heaven," automatically and regardless of whatever else is going on in the economy (Jones (1998, 32-3)). But subsequent investigators have hypothesized and provided evidence that productivity growth and technological progress is endogenous—determined by investment in research and development (R&D). The dependence of technical progress on R&D is a key feature of recent theoretical ("endogenous growth") models (Romer (1990)).

Griliches proposed the following model to incorporate endogenous (R&D-generated) technical change into the production function:

$$Y = F(K, N, Z) \qquad (3)$$

where

Z = the stock of "knowledge capital"

Like physical capital, knowledge capital is a produced means of production, which accumulates according to the perpetual inventory equation $Z_{t+1} = (1 - \delta_Z)\ Z_t + RD_t$, where δ_Z is the knowledge-capital depreciation rate and RD denotes R&D investment.

There are two ways in which one can use eq. (3) to assess the contribution of knowledge capital to productivity growth. One is to examine the relationship (e.g.,

across industries) between TFP growth and the growth of Z. The other is to examine the relationship between TFP growth and "R&D-intensity" (the ratio of R&D investment to output).[1] Under certain reasonable assumptions, the R&D-intensity coefficient in the TFP regression is an estimate of the marginal product of knowledge capital, and of the rate of return to investment in R&D.[2]

Numerous empirical studies (e.g. Griliches and Lichtenberg (1984), Lichtenberg and Siegel (199?)) have provided strong support for the hypothesis that R&D has contributed significantly to growth in the market value of goods and services produced. But economists believe that the utility, or welfare, of individuals and nations depends not only on the goods and services they consume but also on the amount of (leisure) *time* they have. Leisure time as well as goods are arguments of the utility function. Becker defined an individual's "full income" as the value of goods consumed plus the value of leisure time "consumed". Let us define

$$Y^* = G(Y, L) \qquad (4)$$

where

Y^* = "full income" (or utility)

L = leisure time

A simple linear approximation of this function is:

$$Y^* = Y + p_L L$$

where

p_L = the shadow price of leisure time (relative to the price of goods)

Suppose, for simplicity, that p_l remains constant over time. Then

$$\Delta Y^* = \Delta Y + p_L \Delta L$$

[1] The second approach does not require a long history of R&D investment or an estimate of the initial knowledge-capital stock.

[2] Since capital and labor engaged in R&D are already included in K and N—they are "double counted"—the R&D-intensity coefficient is an estimate of the *excess* return to R&D—the difference between the return to R&D and the return on ordinary investment.

The change in full income is the change in GDP plus the change in the value of leisure time consumed. During the last century, longevity increase has been an important source of increase in the average person's leisure time over the course of the life cycle. Nordhaus (2002) estimated that, "to a first approximation, the economic value of increases in longevity over the twentieth century is about as large as the value of measured growth in non-health goods and services" (p. 17).[3] In other words, his estimates imply that $\Delta Y \approx p_L \Delta L$.

Due to the importance of leisure time in general, and longevity in particular, to economic well-being, we propose replacing GDP in the production function by "full income":

$$Y^* = G(Y, L) = F(K, N, Z) \qquad (5)$$

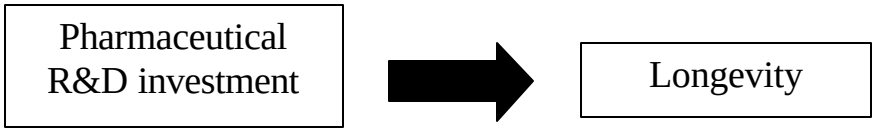
We hypothesize that R&D-generated increases in the stock of knowledge capital (Z) may have a positive impact on *both* components of full income: leisure time (via longevity) and consumption of goods and services. According to the NSF, in 1996 16% of U.S. R&D was associated primarily with the life sciences; this share increased from 12% in 1985.

In the next section we discuss the measurement of pharmaceutical knowledge-capital accumulation. In section 2 we postulate an econometric model of the effect of pharmaceutical knowledge-capital accumulation on the age distribution of deaths. Measurement of changes in the age distribution of deaths, by cause of death, is discussed in section 3. Empirical results are reported in Section 4, and section 5 presents a summary and conclusions.

1. Measurement of pharmaceutical knowledge-capital accumulation

The basic hypothesis we wish to investigate is that pharmaceutical R&D investment has increased the longevity of Americans:

[3] "The Health of Nations: The Contribution of Improved Health to Living Standards," NBER Working Paper No. 8818, February 2002



For a variety of reasons, however, we didn't think that the best way to test this hypothesis is to perform an econometric analysis of the relationship between pharmaceutical R&D investment and longevity. There are two other indicators of pharmaceutical R&D investment that are potentially more fruitful to analyze than pharmaceutical R&D investment itself: pharmaceutical patents, and FDA new drug approvals. We will argue that pharmaceutical patents are subject to most of the same econometric limitations as pharmaceutical R&D investment, but that FDA new drug approval data provide an excellent opportunity to (indirectly) examine the R&D-longevity relationship.

FDA new drug approvals may be interpreted as an "intermediate good" in the R&D-longevity relationship[4]:

To explain the relationship between R&D investment and new drug approvals, and why the latter is a superior indicator for explaining changes in longevity, it is useful to briefly describe the process of drug development.

The FDA's depiction of the new drug development timeline is shown in Figure 1. There are three main phases of drug development up until the time of new drug approval. The first phase is pre-clinical testing, research and development, including testing in animals. According to the FDA, the average duration of this phase is 18 months. In

[4] "FDA estimates that, on average, it takes eight-and-a-half years to study and test a new drug before the agency can approve it for the general public. That includes early laboratory and animal testing, as well as later clinical trials using human subjects. Drug companies spend $359 million, on average, to develop a new drug, according to a 1993 report by the Congressional Office of Technology Assessment." (FDA Center for Drug Evaluation and Research, "From Test Tube to Patient: Improving Health Through Human Drugs," September 1999, p. 15.)

order to proceed to the second stage, the drug sponsor must submit, and receive FDA approval of, an investigational new drug (IND) application. Upon approval of the IND, the sponsor may begin clinical R&D (human trials).

There are three phases of clinical R&D:

Phase	Number of Patients	Length	Purpose	Percent of Drugs Successfully Tested
1	20–100	Several months	Mainly safety	70 percent
2	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	33 percent
3	Several hundred to several thousand	1–4 years	Safety, effectiveness, dosage	25–30 percent

According to the FDA, the average duration of the three phases combined is 5 years.

After completing clinical R&D, the drug sponsor can submit a New Drug Application (NDA) to the FDA. For decades, the regulation and control of new drugs in the United States has been based on the NDA. Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA. According to the FDA, the average duration of the NDA review process is 2 years.

The FDA says that of 100 drugs for which investigational new drug applications are submitted, about 70 percent will successfully complete phase 1 and go on to phase 2; about 33 percent of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing). This is consistent with 1990-2001 data on the number of commercial[5] INDs received and NDAs received and approved shown in Figure 2. The average annual number of NDAs approved (85) was 21% of the average annual number of INDS received (403).

[5] "Commercial INDs" are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. There is another class of filings broadly known as "noncommercial" INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include "Investigator INDs," "Emergency Use INDs," and "Treatment INDs."

As the following table shows, there are seven different kinds of new drug applications:

% of NDAs approved, 1990-2001	NDA Type
46%	New formulation
35%	New molecular entity
10%	New manufacturer
6%	New combination
2%	New ester, new salt, or other noncovalent derivative
1%	New indication[6]
1%	Drug already marketed, but without an approved NDA

New molecular entities (NMEs) account for only about a third of all new drug approvals, but they probably account for the vast majority of pharmaceutical R&D expenditure[7], and they are the NDAs that are most likely to increase longevity.[8]

DiMasi (2001) argues that mean drug development time has increased sharply since the 1960s (see Figure 3). His figures indicate that, for the last 20 years, mean drug development time has been 14.2 years, substantially longer than the FDA's estimate of 8.5 years.

PhRMA provides statistics, based on its annual survey of pharmaceutical firms, on the distribution of 1999 pharmaceutical R&D expenditure by function:

% of 1999 R&D expenditure	Function
10.0%	Synthesis and Extraction
14.2%	Biological Screening and Pharmacological Testing
4.5%	Toxicology and Safety Testing
7.3%	Pharmaceutical Dosage Formulation and Stability Testing
29.1%	Clinical Evaluation: Phases I, II, and III
11.7%	Clinical Evaluation: Phase IV

[6] Beginning in 1994, new indications were tracked as efficacy supplements, not as NDAs.

[7] Cross-sectional firm-level estimates support this hypothesis. When we compute a ("reverse") regression of a firm's average annual R&D expenditure on its average annual number of NDA approvals, by type, the number of NMEs is positive and highly significant, and the number of other NDAs is not significantly different from zero.

[8] 42% of the NMEs approved during 1990-2001 were "priority-review approvals", i.e. considered by the FDA to represent "significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease". Only 14% of non-NME NDAs approved were priority-review approvals.

8.3%	Process Development for Manufacturing and Quality Control
4.1%	Regulatory: IND and NDA
1.8%	Bioavailability
9.0%	Other

These figures suggest that as much as 36% of R&D expenditure occurs during the pre-clinical phase of drug development, which is, on average, (according to DiMasi's estimates) about 8 years before NDA approval. Another 29% of R&D expenditure occurs during the clinical phase, which is, on average, about 5 years before NDA approval. On average, then, the lag from R&D expenditure to new drug approval appears to be quite long, and quite variable.

Long and variable lags is but one of the obstacles to a direct examination of the R&D-longevity relationship. There are several others: apparently inconsistent estimates of pharmaceutical R&D investment, smoothness of the aggregate time-series R&D data, and lack of disaggregated data. We discuss these in turn.

Divergent estimates. There are two distinct surveys that provide data on the amount of pharmaceutical industry R&D: the National Science Foundation (NSF) Survey of Industrial Research and Development[9], and the PhRMA Annual Survey of research-based pharmaceutical companies. Figure 4 shows estimates of aggregate pharmaceutical industry R&D from the two surveys. Before 1990, the estimates differed by less than 10%, but in 1996 and 1997, the estimates differed by about 30%.

Smoothness. To identify the effect of pharmaceutical R&D investment on longevity, significant variability in R&D investment is required. As Figure 4 suggests, aggregate pharmaceutical R&D investment is very closely approximated by an exponential trend, i.e. it exhibits very little variability.[10] This is not surprising: R&D in general is known to be very persistent, especially in comparison with ordinary investment.

Lack of disaggregated data. In principle, variability of R&D investment could be increased via disaggregation, e.g. by class of drugs. Unfortunately, the NSF survey does not provide any disaggregated pharmaceutical R&D investment data. The PhRMA

[9] This survey is administered by the Census Bureau.
[10] The R^2 of the regression of the PhRMA R&D series on an exponential trend is .9913.

survey does, but the drug classes are quite broad; 85% of investment during 1997-1999 was in the largest four classes.

Drug class	**1997**	**1998**	**1999**	**average**
Acting on the central nervous system and sense organs	29%	30%	23%	27%
Affecting neoplasms, endocrine system, and metabolic diseases	24%	23%	24%	23%
Acting on infective and parasitic diseases	22%	22%	14%	19%
Acting on the cardiovascular system	17%	17%	15%	16%
Acting on the respiratory system	6%	4%	4%	5%
Other human use	0%	0%	10%	3%
Biologicals	0%	3%	5%	3%
Acting on the digestive or genitourinary system	0%	0%	4%	1%
Diagnostic agents	2%	1%	0%	1%
Acting on the skin	0%	0%	1%	0%
Vitamins and nutrients	0%	0%	0%	0%

Are patent data likely to be useful? R&D and patenting are known to be closely related.[11] Perhaps patent data could supersede most of the limitations of the R&D data.

The U.S. Patent and Trademark Office (USPTO) publishes data on the number of patents granted for "drug, bio-affecting and body treating compositions" (patent class 514). Figure 5 presents annual data on the number of "drug patents" (patents in class 514) and total patents granted from 1980 to 2000. Drug patents do exhibit somewhat more variability than R&D expenditure.[12] However drug patents track total patents quite closely.

Disaggregation of drug patents by therapeutic action appears to be infeasible. Although certain subclasses of class 514 pertain to specific diseases (e.g. subclass 866 refers to diabetes, and subclass 883 refers to Hodgkin's disease[13]), these subclasses are "cross-reference art collections", and drug patents are not systematically classified by disease or therapeutic action.[14]

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[11] See *R&D, Patents, and Productivity*, ed. by Zvi Griliches.

[12] The R^2 of the regression of the drug patent series on an exponential trend is .8897.

[13] See http://www.uspto.gov/go/classification/uspc514/sched514.htm.

[14] The seventh (1999) edition of the International Patent Classification system appears to provide (in class A61P) a systematic classification of chemical compounds and medicinal preparations by therapeutic activity. For example subclass 1/ 00 includes drugs for disorders of the alimentary tract or the digestive

It appears that drug patents are often granted fairly early in the drug development cycle. According to PhRMA, "the average period of effective patent life (when a drug can be marketed) for new drugs introduced in the early to mid-1990s with patent-term restoration has been only 11-12 years. Innovators in other industries typically receive upwards of 18.5 years of effective patent life."[15] This suggests that, on average, patents are granted at least seven years prior to the market introduction of new drugs. Long and variable lags diminish the likelihood that drug patents can explain fluctuations in longevity.

Data on both pharmaceutical R&D expenditure and pharmaceutical patents are too aggregated, exhibit too little variability, and are subject to excessively long lags to serve as a basis for testing our key hypothesis. But these limitations may be overcome by combining data from two different sources: First DataBank's National Drug Data File (NDDF)[16], and FDA data on NDA approvals[17]. These data sources enable us to compute the stock of drugs available (i.e., previously approved by the FDA) to treat a given condition in a given year.

The NDDF consists of a number of modules. One of these is the indications module, "the goal of [which] is to minimize the risks associated with drug use. The information in this module is intended to be used as a tool for assessing the appropriateness of drug therapy." We utilize just one part of the clinical module: the Drug Indications Master Table. This table links indications (diseases) to drugs (active

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system, and subclass 1/18 covers drugs for pancreatic disorders, e.g. pancreatic enzymes. (See http://www.wipo.int/classifications/fulltext/new_ipc/index.htm.)

[15] http://www.phrma.org/publications/publications/profile01/chapter8.phtml.

[16] First DataBank, a wholly owned subsidiary of The Hearst Corporation, is a leading provider of electronic drug information. For more than two decades, it has delivered knowledge bases for various healthcare applications, including clinical decision support within the workflow. Its portfolio also includes comprehensive reference products; integrated content software; and specialty software for physicians and nutritionists. Many of these products help reduce the incidence of medication errors and adverse drug events, which can result in shorter hospital stays, lower medical costs, and improved patient care. The NDDF Plus knowledge base combines the drug information of the National Drug Data File with advanced clinical decision-support modules, to deliver complete descriptive, pricing and clinical information for every drug approved by the FDA. Their staff includes clinicians, software engineers and knowledge base experts. It is found in installations ranging from retail pharmacies to hospital pharmacies and laboratories; physician and other healthcare professional practices; as well as e-healthcare companies, managed care organizations and insurers.

[17] Section 505 of the Federal Food, Drug, and Cosmetic Act states that "no person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application…is effective with respect to such drug."

ingredients): it lists all of the drugs appropriate for treatment of each indication. Indications are coded using the International Classification of Diseases, Ninth Revision (ICD9)[18], the same classification system used in the mortality data we will analyze.[19]

Sample data from the NDDF Drug Indications Master Table, for two indications—tuberculosis and hypercholesterolemia—are shown in Table 1.[20] The table lists 11 drugs appropriate for the treatment of tuberculosis, and 14 drugs appropriate for the treatment of hypercholesterolemia. All of the tuberculosis drugs are designated as "labeled", but three of the hypercholesterolemia drugs are designated as "unlabeled".[21] According to the American Medical Association's Council on Scientific Affairs,

> Unlabeled uses are defined as the use of a drug product for indications or in patient populations, doses, or routes of administration that are not included in FDA-approved labeling. The prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial. Unlabeled indications are especially common in oncology, rare diseases, and pediatrics. Thus, the prescribing of drugs for unlabeled uses is often necessary for optimal patient care.[22]

We will construct estimates of the stock of drugs available to treat specific conditions, both excluding and including unlabeled indications.

The NDDF Drug Indications Master Table lists all of the drugs appropriate for treating given conditions that were available *in the year 1999*.[23] We want to determine the number of drugs appropriate for treating given conditions that were available *in each of the years 1979-1998* (the years for which we have mortality data). To determine this,

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[18] The International Classification of Diseases (ICD) is designed for the classification of Morbidity and Mortality information for statistical purposes, and for the indexing of hospital records by disease and operations, for data storage and retrieval. The International Classification of Disease is developed collaboratively between the World Health Organization (WHO) and 10 international centers, for purposes of ensuring that medical terms reported on death certificates are internationally comparable and lend themselves to statistical analysis. The ICD has been revised approximately every 10 years since 1900 in order to reflect changes in understanding of disease mechanisms and in disease terminology.

[19] Information about drugs appropriate for treatment of specific indications can be obtained on a piecemeal basis from http://www.medscape.com.

[20] The complete Drug Indications Master Table contains almost 7000 links between indications and drugs.

[21] About 25% of the almost 7000 entries in the Drug Indications Master Table are designated "unlabeled".

[22] http://www.ama-assn.org/ama/pub/article/2036-2420.html. See also Cranston JW, Williams MA, Nielsen NH, Bezman RJ, for the Council on Scientific Affairs. "Unlabeled indications of Food and Drug Administration-approved drugs," *Drug Information Journal*. 1998; 32:1049-1061.

[23] Unfortunately, earlier versions of the NDDF Drug Indications Master Table are not available.

we identified, from published and unpublished FDA data, the year in which each of the drugs listed in the NDDF Drug Indications Master Table was first approved as a New Molecular Entity (NME) by the FDA. The FDA provided us with a list of all 821 NMEs approved by the FDA during the period 1950-1993. We extended this list through 1998 using another unpublished FDA data file and data posted on the FDA website. The FDA data on NME approvals are illustrated in Table 2, which shows NMEs approved in calendar year 2000.

We aggregated the data in the NDDF Drug Indications Master Table up to the (approximately) 2-digit ICD9 level, to be consistent with the CDC Mortality Data (described below). There is considerable variation across diseases—even diseases in the same broad disease groups—in the extent and timing of increases in the stock of available drugs. This is illustrated by Figure 6, which shows, for two conditions—diseases of the thyroid gland and diseases of other endocrine glands—the number of drugs available to treat the condition in year t, as a percent of the number of drugs available to treat the condition in 1979.[24] Between 1979 and 1984, the number of drugs available to treat diseases of the thyroid gland increased 29%, while the number of drugs available to treat diseases of other endocrine glands increased only 13%. However, between 1984 and 1998, the number of drugs available to treat diseases of the thyroid gland did not increase at all, while the number of drugs available to treat diseases of other endocrine glands increased 33%.

The algorithm we adopted is based on the assumption that a drug linked to a condition in the NDDF Drug Indications Master Table became available to treat the condition in the year that the drug was first approved as an NME by the FDA. We know that this assumption is incorrect in at least some cases, because some of a drug's indications may be added years after the drug was first approved as an NME. Table 3 provides examples of New Indication approvals, and the predecessor NME approvals. Amantadine hydrochloride was initially approved as an NME in 1966, and designated as an antiviral/anti-influenza/systemic drug. Seven years later, a new indication of the drug was approved by the FDA, and it was also classified as an anti-parkinson drug.

[24] In 1979, there were 7 drugs for treating diseases of the thyroid gland, and 38 drugs for treating diseases of other endocrine glands

Unfortunately, although we have complete data on NME approvals, data on New Indication approvals are incomplete. Even if complete data on New Indication approvals by the FDA were available, in light of extensive unlabeled drug use, it is not clear how they should be used. A drug approved as an NME might be frequently prescribed for many years for a condition that is "off-label".

When the FDA receives a New Drug Application, it assesses the drug's "therapeutic potential", and classifies it as either a "Priority Review" drug—one that represents a "significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease"—or a "Standard Review" drug—one that "appears to have therapeutic qualities similar to those of one or more already marketed drugs."[25] Two diseases that have similar increases in the total number of NMEs approved may have quite different increases in the number of priority review NMEs approved. For example, 16 drugs for treating syphilis were approved during 1979-1998, but only 5 (31%) of these were priority review drugs. The total number of drugs approved for treating lymph cancer was lower—14—but 10 (71%) of these drugs were priority review drugs. In our empirical analysis, we will distinguish between the stock of priority review drugs available to treat a condition and the stock of standard review drugs available.

2. Model

The basic model we will estimate is:

$$MORT_{it} = \beta\ DRUG\_STOCK_{it} + \alpha_i + \delta_t + \varepsilon_{it} \qquad (6)$$

where:

$MORT_{it}$ = an indicator of mortality (e.g., mean age at death) from ICD9 disease i (i = 00, 01, …, 99) in year t (t = 1979, 1980,…, 1998)

$DRUG\_STOCK_{it}$ = the stock of drugs available to treat disease i in year t

[25] Applications for new indications are also classified by therapeutic potential, and the therapeutic potential of a new indication may differ from the therapeutic potential of the NME.

The fixed disease effects (α_i's) control for any determinants of mortality that vary across diseases but do not vary over time. The year effects (δ_t's) control for any determinants of mortality that vary over time but do not vary across diseases. If the estimate of β is positive and significant, that indicates that diseases with *above-average* increases in the stock of drugs had *above-average* changes in the mortality indicator.

We can allow for different effects of priority-review and standard-review drug approvals by estimating the more general model:

$$MORT_{it} = \beta_P \, PRI\_STOCK_{it} + \beta_S \, STD\_STOCK_{it} + \alpha_i + \delta_t + \varepsilon_{it} \qquad (7)$$

where:

PRI_STOCK_{it} = the stock of priority-review drugs available to treat disease i in year t

STD_STOCK_{it} = the stock of standard-review drugs available to treat disease i in year t

We think it is worthwhile to briefly discuss how this model relates to the literature on endogenous technical change and on embodiment.

Endogenous technical change model. In Romer's (1990) model of endogenous technological change, labor is used to produce either output or ideas:

$$L = L_Y + L_A$$

where

L = total labor
L_Y = labor used to produce output
L_A = labor used to produce ideas

The production function for output is:

$$Y = K^{\alpha}(A \, L_Y)^{1-\alpha} \qquad (0 < \alpha < 1)$$

where:

Y = output

K = capital
A = stock of ideas

The production function for ideas is:

$$\Delta A = A_{+1} - A = \delta L_A^{\lambda} A^{\phi}$$

where $0 < \lambda \leq 1$ and ϕ may be either positive or negative. The DRUG_STOCK variable corresponds to Romer's "stock of ideas" variable (A). In the empirical analysis, we count only the "ideas" (new molecular entities) that have been approved by the FDA.

While the model we will estimate is consistent with Romer's embodied technical change model, there are other ways in which one might specify the drugs-mortality relationship. New products and ideas do not diffuse instantaneously throughout the economy or health care system. After new drugs are introduced, some people continue to use old drugs. Hence measures of the *vintage distribution of drugs used* to treat a given disease in a given year might be preferable to a simple count of the *number of drugs available* to treat the disease. In practice, however, measurement of the vintage distribution of drugs used by disease and year is far more difficult than measurement of the number of drugs available by disease and year. Vintage data can be constructed from the National Ambulatory Medical Care Survey (NAMCS), a survey of physician office visits that collects data on patient diagnoses and drugs prescribed. Unfortunately, prior to 1989, it was conducted in only three years: 1980, 1981, and 1985.[26] NAMCS is an approximately 1-in-10,000 survey of office visits, so it is subject to considerable sampling error. More than one diagnosis is recorded in a significant number of visits; in these cases it is difficult to allocate or assign drugs to diseases. Drug vintages are subject to left-censoring: the vintages of drugs that existed prior to the creation of the FDA in 1939 can't be determined. Finally, interpretation of the coefficient on the number of drugs available is perhaps more straightforward than interpretation of the coefficient on the mean age of drugs used.

Embodiment. Implicit in this specification is the hypothesis that the technical progress generated by pharmaceutical R&D is *embodied* in new drugs. Solow and other economists have recognized since the late 1950s that there are two kinds of technical

[26] It has been conducted annually since 1989.

progress: *disembodied* and *embodied*. Suppose that agent i in the economy (e.g. a firm or government agency) engages in research and development. If technical progress is disembodied, another agent (j) can benefit from agent i's R&D whether or not he purchases agent i's products. But if technical progress is embodied, agent j benefits from agent i's R&D only if he purchases agent i's products. Solow conjectured that most technical progress was embodied. In one paper (Solow (1962, p. 76)), he assumed that "*all* technological progress needs to be 'embodied' in newly produced capital goods before there can be any effect on output."

A number of econometric studies have investigated the hypothesis that capital equipment employed by U.S. manufacturing firms embodies technological change, i.e. that "each successive vintage of investment is more productive than the last." Equipment is expected to embody significant technical progress due to the relatively high R&D-intensity of equipment manufacturers. According to the National Science Foundation, the R&D-intensity of machinery and equipment manufacturing is about 50% higher than the R&D-intensity of manufacturing in general, and 78% higher than the R&D intensity of all industries.

One method that has been used to test the equipment-embodied technical change hypothesis is to estimate manufacturing production functions, including (mean) vintage of equipment as well as quantities of capital and labor. Bahk and Gort (1993) argued that "we can take due account of the effect of vintage by measuring the average vintage of the stock" (p. 565). Similarly, Sakellaris and Wilson (2000) stated that "a standard production function estimation (in logs) provides an estimate of embodied technical change by dividing the coefficient on average age [of equipment] by the coefficient on capital stock" (capital's share in total cost).

These studies have concluded that technical progress embodied in equipment is a major source of manufacturing productivity growth. Hulten (1992) found that as much as 20 percent (and perhaps more) of the BLS total-factor-productivity change (in manufacturing) can be directly associated with embodiment—the higher productivity of new capital than old capital. For equipment used in U.S. manufacturing, best-practice technology may be as much as 23 percent above the average level of technical efficiency.

Bahk and Gort (1993) concluded that "Industrywide learning appears to be uniquely related to embodied technical change of physical capital. Once due account is taken of the latter variable, residual industrywide learning [disembodied technical change] disappears as a significant explanatory variable" (p. 579). And Sakellaris and Wilson (2000) estimate that "each vintage is about 12 percent more productive than the previous year's vintage (in the preferred specification)", and that equipment-embodied technical change accounted for about two thirds of U.S. manufacturing productivity growth between 1972 and 1996.

Estimation of eqs. (6) and (7) enables us to test the pharmaceutical-embodied technical progress hypothesis—the hypothesis that newer drugs increase longevity—and to estimate the contribution of new drugs to longevity increase.

One might be concerned that estimation of these equations could result in overestimation of the average longevity impact of pharmaceutical innovation. Suppose that the expected effect of a new drug on mean age at death is higher for some diseases than for others: instead of a single β in eq. (6), there is a distribution of β_i's. One might hypothesize that pharmaceutical companies would devote most of their research budgets to diseases where the expected effect of a new drug on mean age at death is highest, and therefore that most new drugs would be developed for such diseases. However a more rational investment strategy would be to invest heavily in diseases where the *total* (as opposed to *average*) expected increase in life-years is greatest. Suppose that the expected effect of a new drug on mean age at death from disease A is 6 months, and that the expected effect of a new drug on mean age at death from disease B is 1 month. If 10 times as many people suffer from disease B as from disease A, then the social (and presumably private) benefits to investment in disease B is higher, even though the benefit per patient is lower. Since firms will not necessarily invest more in diseases with high benefits per patient[27], it is not obvious that the estimate of β will be an overestimate of the (weighted) mean of the β_i's (weighted by number of new drugs).

[27] In 1983, Congress passed the Orphan Drug Act, in an attempt to encourage firms to develop drugs for the treatment of rare diseases (diseases borne by fewer than 200 thousand Americans). See Lichtenberg, Frank, and Joel Waldfogel, "Does Misery Love Company? Evidence from Pharmaceutical Markets Before and After the Orphan Drug Act," working paper, 2002.

Other medical innovations. In 1995, pharmaceutical R&D accounted for more than half, and perhaps as much as two thirds, of industry funding for health R&D.[28] New drugs are not the only type of medical innovation that might be hypothesized to contribute to longevity increase. Another important kind of innovation, and one that is also regulated by the FDA, is medical devices. If a company seeks to market a medical device, FDA approval of a Premarket Approval Application (PMA) is required. Premarket approval by the FDA is the required process of scientific review to ensure the safety and effectiveness of all devices classified as Class III devices. The FDA maintains a PMA database (http://www.fda.gov/cdrh/pmapage.html). From this database, one can construct estimates of the number of PMA approvals, by various characteristics. Figure 7 shows the number of original PMAs reviewed by the FDA during the period 1981-2001. One characteristic is the identity of the Advisory Committee that has jurisdiction over the device. As Table 4 indicates, there are nineteen Advisory Committees, but two committees account for more than half of all original PMAs.[29] Moreover, it would be difficult to construct a "mapping" from PMAs classified by Advisory Committee to mortality data classified by ICD9 code. PMAs are also classified by "Product Code", but the number of distinct Product Codes is extremely large (almost as large as the number of PMAs--over 5000), they do not appear to be hierarchically organized, and it would be difficult to construct a "mapping" from Product Codes to ICD9 codes. (Unfortunately, neither First DataBank nor anyone else produces a *Device* Indications Master Table.)[30]

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[28] According to data compiled by the National Institutes of Health, in 1995, industry funding for health R&D was equal to $18,645 million. (http://www.cdc.gov/nchs/products/pubs/pubd/hus/tables/2001/01hus126.pdf) The National Science Foundation reports that company-funded R&D in drugs and medicines in that year was $10,202 million, and PhRMA reports that domestic U.S. R&D by pharmaceutical firms was $11,874 million.

[29] Over 90% of PMAs are "supplemental" PMAs: applications to modify the design, manufacturing, or other aspects of original PMAs.

[30] The PMA database includes "device description / indications" information, but disease coding of this information would be challenging and costly. Here is sample information about PMA Number P010054, Approval for the Elecsys Anti-HBs Immunoassay and Elecsys PreciControl Anti-HBs: "The Elecsys Anti-HBs Immunoassay is indicated for: The qualitative determination of total antibodies to the hepatitis B surface antigen (HBsAg) in human serum and plasma (EDTA). The electrochemilumin-escence immunoassay "ECLIA" is intended for use on the Roche Elecsys 2010 immunoassay analyzer. Assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection. A reactive assay result will allow a differential diagnosis in individuals displaying signs and symptoms of hepatitis in whom etiology is unknown. The detection of anti-HBs is indicative of

Suppose that mortality from disease i in year t depends on the stocks of both drugs and devices approved to treat that disease. We can measure the stock of drugs, but due to the data limitations just described, we cannot measure the stock of devices. If changes in the stock of devices are uncorrelated across diseases with changes in the stock of drugs, the drug-stock coefficient is unbiased. If changes in the stocks of devices and drugs are correlated, the drug-stock coefficient is biased. The direction of bias depends on the sign of the correlation. If the change in the stock of devices is negatively correlated across diseases with the change in the stock of drugs, the drug-stock coefficient is downward biased. Some evidence suggests that this correlation may indeed be negative. Lichtenberg (1996, 2001) presented evidence that use of newer drugs is associated with lower utilization of hospital care. Since use of some medical devices, such as stents and artificial hearts, requires hospitalization, drugs and devices may be substitutes rather than complements.

3. Measurement of changes in the age distribution of deaths, by cause of death

We used the Compressed Mortality File (CMF) to measure changes in the age distribution of deaths, by cause of death. The CMF is a county-level national mortality and population data base spanning the years 1968-1999, produced by the Office of Analysis and Epidemiology, National Center for Health Statistics, Centers for Disease Control and Prevention. The mortality database of the CMF is derived from the U.S. records of deaths that occurred in 1979-1999.

Deaths are classified by *underlying cause*. The person completing the death certificate is instructed to report, according to his or her best medical opinion, "the chain of events leading directly to death, proceeding from the *immediate cause* of death (the final disease, injury, or complication directly causing death) to the *underlying cause* of death (the disease or injury that initiated the chain of morbid events which led directly to

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laboratory diagnosis of seroconversion from hepatitis B virus (HBV) infection. The Elecsys PreciControl Anti-HBs is indicated for: The preciControl Anti-HBs is used for quality control of the Elecsys Anti-HBs immunoassay on the Elecsys 2010 immunoassay analyzer. The performance of the PreciControl Anti-HBs has not been established with any other Anti-HBs assay."

death)."[31] For example, Part I of the cause-of-death section of the certificate might be completed in the following way:

		Approximate interval between onset and death
	Rupture of myocardium (immediate cause)	minutes
Due to (or as a consequence of):	Acute myocardial infarction	6 days
Due to (or as a consequence of):	Chronic ischemic heart disease (underlying cause)	5 years

The system used to classify deaths changed in 1979 and again in 1999. The three classification schemes are different enough so as to make direct comparisons of cause of death difficult, so our analysis is confined to the period 1979-1998.[32]

Counts and rates of death can be obtained by place of residence (U.S., state, and county), age, race (white, black, and other), gender, year, and underlying cause-of-death (4-digit ICD code or group of codes). There are 17 age groups: under 1 day, 1 - 6 days, 7 - 27 days, 28 - 364 days, 1 - 4 years, 5 - 9 years, 10 - 14 years, 15 - 19 years, 20 - 24 years, 25 - 34 years, 35 - 44 years, 45 - 54 years, 55 - 64 years, 65 - 74 years, 75 - 84 years, over 85 years, and unknown. We excluded infant deaths (age less than 1 year) and deaths at unknown ages. For each approximately 2-digit ICD9 code and year, we calculated two statistics: mean age at death[33], and the fraction of deaths that occurred before age 65.

Data on the number of deaths, population, and the crude death rate, by age group for 1979 and 1998 are presented in Table 5. The crude death rate declined in every age group except the highest (over 85 years). Despite this, the crude death rate for the entire population increased, due to aging of the population. The fraction of deaths occurring before age 65 decreased from 32% in 1979 to 24% in 1998.

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[31] CDC, "Instructions for completing the cause-of-death section of the death certificate," http://www.cdc.gov/nchs/data/dvs/cod.pdf

[32] Data for 1979-1999 are available at the website http://wonder.cdc.gov/mortsql.shtml.

[33] We assumed that deaths in a given age interval occurred at the mean of the lower and upper ages of the interval, e.g. deaths at ages 1-4 occurred at age 2.5. We assumed that deaths at ages greater than 85 occurred at age 89.5.

Figure 8 shows a comparison of mean age at death (from all causes) to life expectancy at birth over the period 1979-1997.[34] Life expectancy at birth is higher than mean age at death. For example, in 1997 life expectancy at birth was 76.5 years, and mean age at death was 71.9 years. However the 1979-1997 increase in mean age at death (4.0 years) was greater than the increase in life expectancy at birth (2.6 years).

4. Empirical Results

Estimates of equations (6) and (7) are presented in Table 6. All equations are estimated via weighted least squares, where the weight is equal to the number of deaths. In the first column, the dependent variable is mean age at death, drugs not labeled for a given indication are excluded, and we do not distinguish between priority-review and standard-review drugs. The coefficient on the total stock of drugs is positive but only marginally significant (p-value=.11). The second column is the same, except that unlabeled drugs listed in the NDDF Drug Indications Master Table are included. This has a modest positive effect on the point estimate of β, but reduces its standard error, so that the estimate is now highly significant (p-value=.02). This is consistent with the AMA Council on Scientific Affairs' observation that "the prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial," and with the hypothesis that increases in the stock of (labeled and unlabeled) drugs to treat a condition increase the mean age at which people die from that condition.

[34] Source: Anderson, Robert (1999). United States life tables, 1997. National vital statistics reports; vol 47 no. 28. Hyattsville, Maryland: National Center for Health Statistics. Life expectancy (e_x)--the average number of years of life remaining for persons who have attained a given age (x)--is the most frequently used life table statistic. Calculation of the complete life table is derived from the probability of death (q_x), which depends on the number of deaths (D_x) and the midyear population (P_x) for each single year of age (x) observed during the calendar year of interest. There are two types of life tables—the generation or cohort life table and the current life table. The current life table (upon which these life expectancy figures are based) does not represent the mortality experience of an actual cohort. Rather, the current life table considers a hypothetical cohort and assumes that it is subject to the age-specific death rates observed for an actual population during a particular period. Thus, for example, a current life table for 1997 assumes a hypothetical cohort subject throughout its lifetime to the age-specific death rates prevailing for the actual population in 1997. The current life table may thus be characterized as rendering a ''snapshot'' of current mortality experience, and shows the long-range implications of a set of age-specific death rates that prevailed in a given year.

In the equations reported in columns 3 and 4, the dependent variable is an alternative statistic of the age distribution of deaths: the fraction of deaths that occur before the age of 65. These estimates seem to confirm the estimates in the first two columns: when unlabeled indications are excluded, β is insignificantly different from zero, but when they are included, β is negative and highly significant, indicating that increases in the stock of drugs reduce the probability of dying before the age of 65.

In columns 5 and 6, the dependent variable is again mean age at death, but the stock of drugs is classified by therapeutic potential, i.e. disaggregated into priority-review and standard-review drugs. Whether or not unlabeled indications are included, β_P (the coefficient on the stock of priority-review drugs) is positive and highly significant, and β_S (the coefficient on the stock of standard-review drugs) is insignificantly different from zero. This is not surprising, since, as discussed earlier, priority-review drugs are those that represent a "significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease," while standard-review drugs are those that "appear to have therapeutic qualities similar to those of one or more already marketed drugs." Once again, the estimate of β_P is larger and more significant when unlabeled indications are included than it is when they are excluded.

Columns 7 and 8 report analogous regressions, in which the dependent variable is the fraction of deaths that occur before the age of 65. Once again, we cannot reject the null hypothesis that the stock of standard-review drugs has no effect on mortality, but the hypothesis that the stock of priority-review drugs has no effect on mortality can be rejected, especially when unlabeled indications are included.

Since β_S is not significant in any equation in columns 5-8, in columns 9-12 we estimate models that include *only* the stock of priority-review drugs. The estimates of β_P in columns 9-12 are fairly similar to their counterparts in columns 5-8. We will use the estimate of β_P in column 10 to evaluate the contribution of pharmaceutical knowledge-capital accumulation to the increase in the mean age at death during the period 1979-1998.

Sample mean[35] values of the dependent and independent variable in 1979 and 1998 are as follows:

year	AGE_DEATH	PRI_STOCK
1979	69.6	4.6
1998	73.4	10.6
change	3.8	6.0

Mean age at death increased by 3.8 years from 1979 to 1998: ΔAGE_DEATH = 3.8 years. The mean stock of priority-review drugs increased by 6.0 drugs: ΔPRI_STOCK = 6.0 drugs. The estimated contribution of the increase in the stock of priority-review drugs to the increase in mean age at death is β_P * ΔPRI_STOCK = .065 * 6.0 = 0.39 years. The increase in the stock of priority-review drugs is estimated to have increased mean age at death by 0.39 years (4.7 months) during this period. Hence, about 10 percent of the total increase in mean age at death is due to the increase in the stock of priority-review drugs.[36]

Now we will attempt to compare the value of the longevity benefit of pharmaceutical knowledge-capital accumulation to its cost. During the period 1979-1998, 508 NMEs (about 25/year) were approved by the FDA. The Office of Technology Assessment estimated that the average cost of an NME approval is $359 million, so the total cost of pharmaceutical knowledge-capital accumulation during the period was 508 NMES * $359 million/NME = $182 billion.[37]

The increase in the stock of priority-review drugs is estimated to have increased mean age at death by 0.39 years during this period. There are about 2 million deaths per year, so the total number of life-years gained per year is 0.39 * 2 million = 800,000 life-years/year. A number of authors have estimated that the value of a life-year is in the neighborhood of $150,000. Hence the value of the annual gain in life-years is 800,000 * $150,000 = $120 billion. Presumably, knowledge capital does not depreciate (although it

[35] These are weighted means, weighted by the number of deaths.
[36] This estimate may be conservative, because it includes only the *within-disease* increase in mean age at death. We estimate that about 19% of the overall increase in mean age at death was due to a *shift* in the distribution of fatal diseases. Approval of new drugs may have contributed to this shift as well as to the within-disease increase in mean age at death.
[37] This is the cost of *all* NMEs approved—both priority-review and standard-review. About 40% of NMEs are priority-review NMEs.

can be rendered obsolete by future knowledge capital accumulation), so even if no new drugs were approved after 1998, people would continue to experience the 0.39-year higher life expectancy in all future years. In other words, the $120 billion may be viewed as an annuity.

As noted earlier (Figure 3), DiMasi estimates that, in the last two decades, drug development has taken about 14 years. Suppose that the $182 billion in R&D expenditure is evenly distributed over an initial 14-year period, i.e. $13 billion/year in years 1-14. In year 15 and all future years, the population experiences a gain in life-years whose annual value is $120 billion. The internal rate of return to this series of cash flows is 18%.

5. Summary and Conclusions

People value leisure time as well as goods, so longevity increase is an important part of economic growth, broadly defined. R&D is the principal source of economic growth, and the pharmaceutical industry is the most R&D-intensive sector of the economy. In this paper we have assessed the contribution of pharmaceutical R&D to longevity increase (hence to economic growth), by analyzing the relationship between FDA approvals of new molecular entities and changes in the age distribution of deaths, using longitudinal disease-level data.

We computed the stock of drugs available (i.e., previously approved by the FDA) to treat a given condition in a given year by combining FDA data with data from First DataBank's National Drug Data File. We used the CDC's Compressed Mortality File to measure changes in the age distribution of deaths, by cause of death.

The estimates indicated that approval of standard-review drugs—drugs whose therapeutic qualities the FDA considers to be similar to those of already marketed drugs—has no effect on longevity, but that approval of priority-review drugs—those considered by the FDA to offer significant improvements in the treatment, diagnosis, or prevention of a disease—has a significant positive impact on longevity. Increases in the stock of (labeled and unlabeled) drugs to treat a condition increase the mean age at which people die from that condition, and reduce the probability of dying before the age of 65.

The increase in the stock of priority-review drugs is estimated to have increased mean age at death by 0.39 years (4.7 months) during the period 1979-1998. Ten percent of the total increase in mean age at death was due to the increase in the stock of priority-review drugs. The rate of return on investment in pharmaceutical R&D is 18%. This rate of return reflects only the value of increased longevity among Americans; foreigners also benefit, and evidence[38] suggests that there may be additional benefits of new drugs to Americans, including reduced hospital expenditure and reduced limitations on work and other activities.

[38] Lichtenberg, Frank, "Are the Benefits of Newer Drugs Worth Their Cost? Evidence from the 1996 MEPS," *Health Affairs* 20(5), September/October 2001, 241-51, and Lichtenberg, Frank, and Suchin Virabhak, "Pharmaceutical-embodied technical progress, longevity, and quality of life: drugs as 'equipment for your health,'" working paper, Columbia University, Dec. 2001.

Figure 1

New Drug Development Timeline

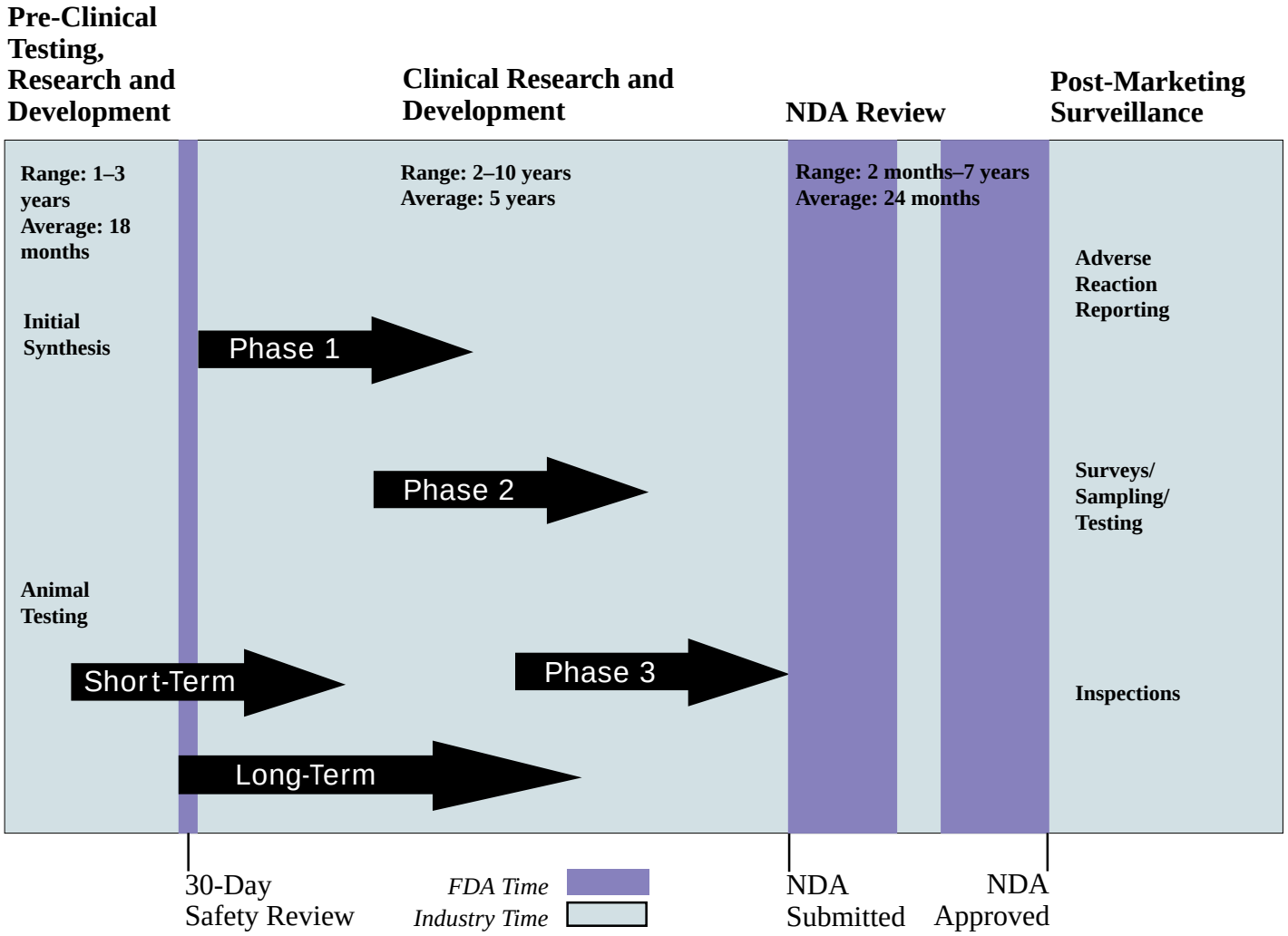


Figure 2
Commercial INDs received and NDAs received and approved, 1990-2001

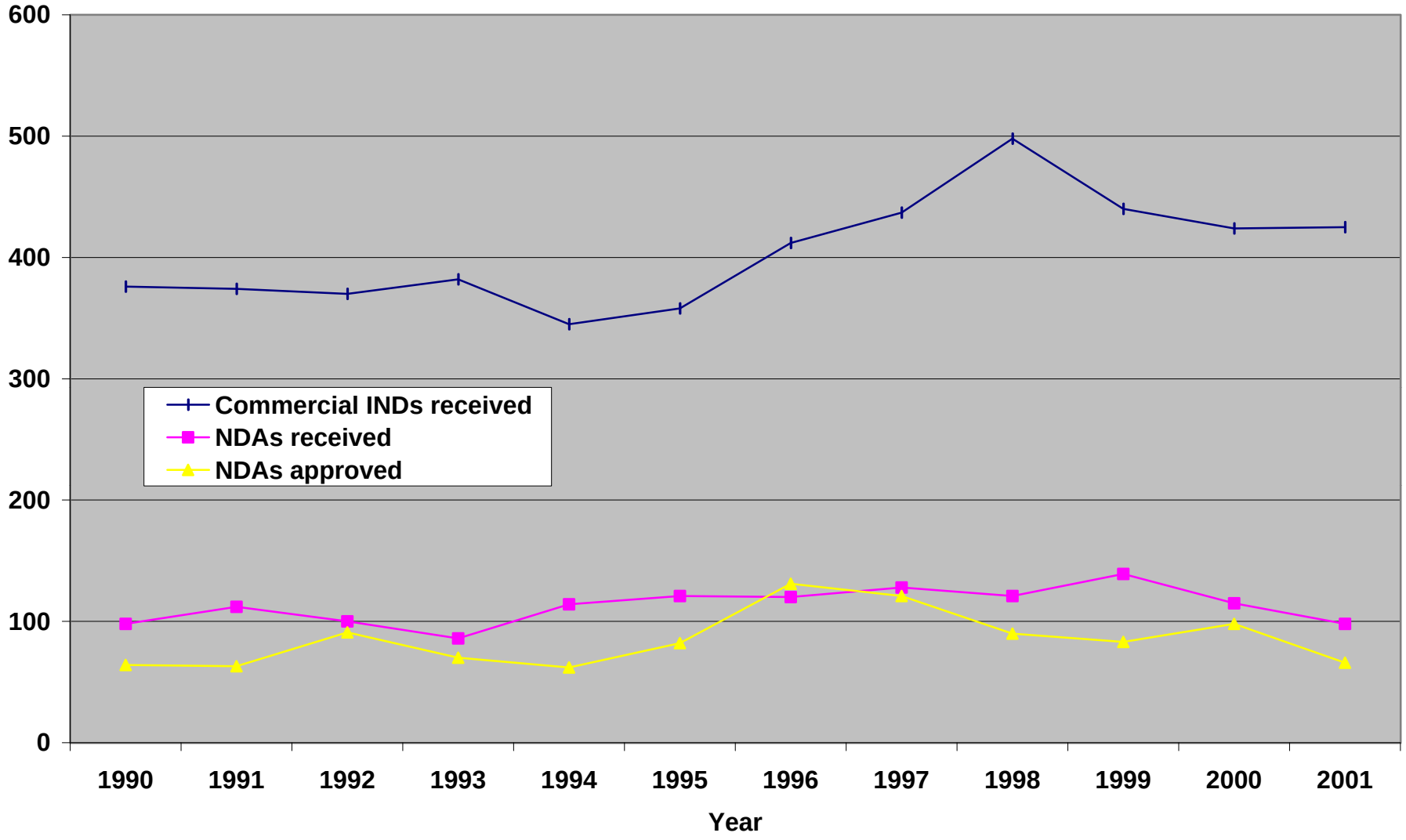
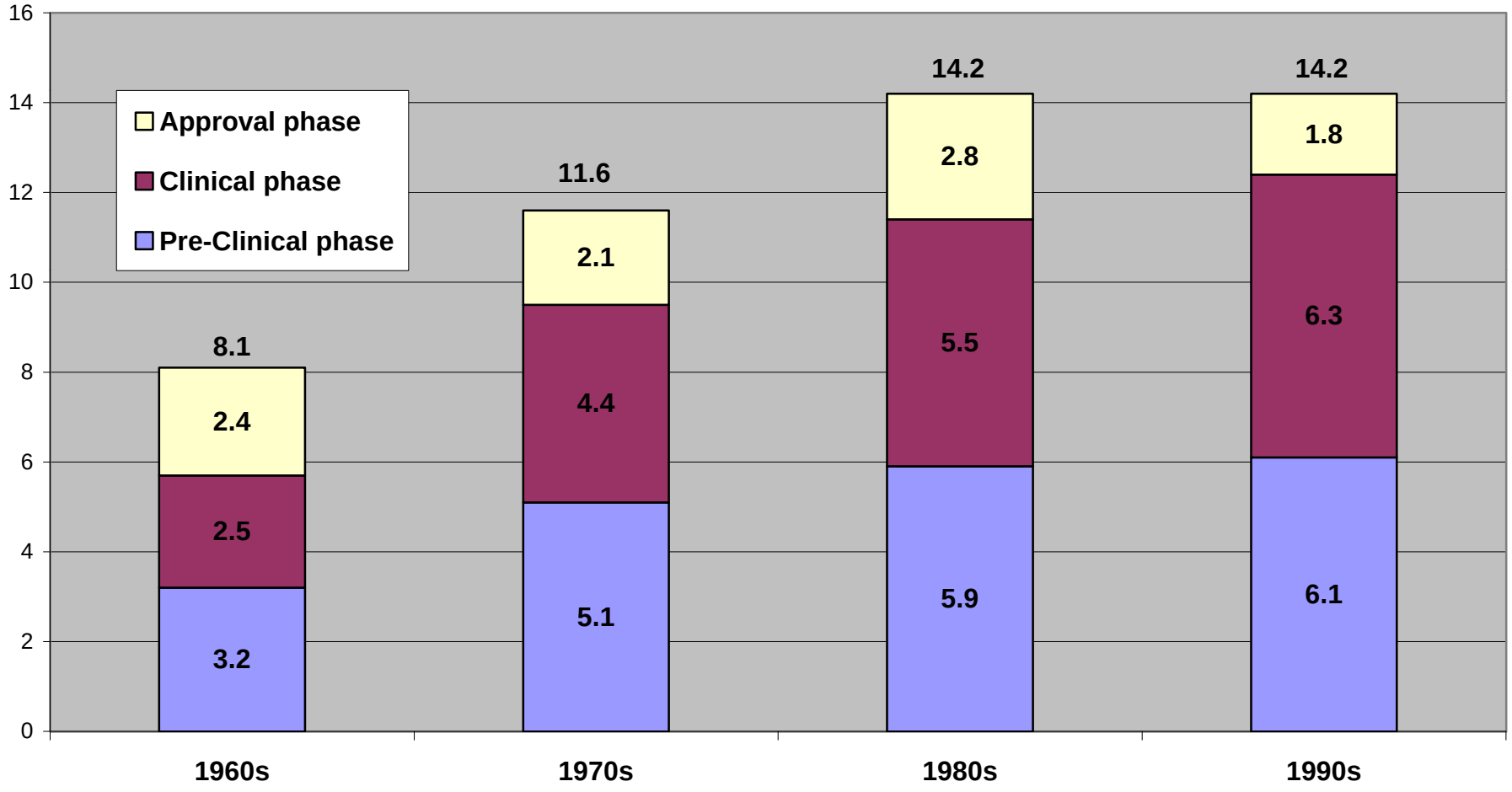


Figure 3
Average number of years for drug development, 1960s to 1990s



Source: DiMasi, J.A., "New Drug Development in US 1963-1999," Clinical Pharmacology and Therapeutics 2001, May

Figure 4
Estimates of aggregate pharmaceutical industry R&D from NSF and PhRMA surveys

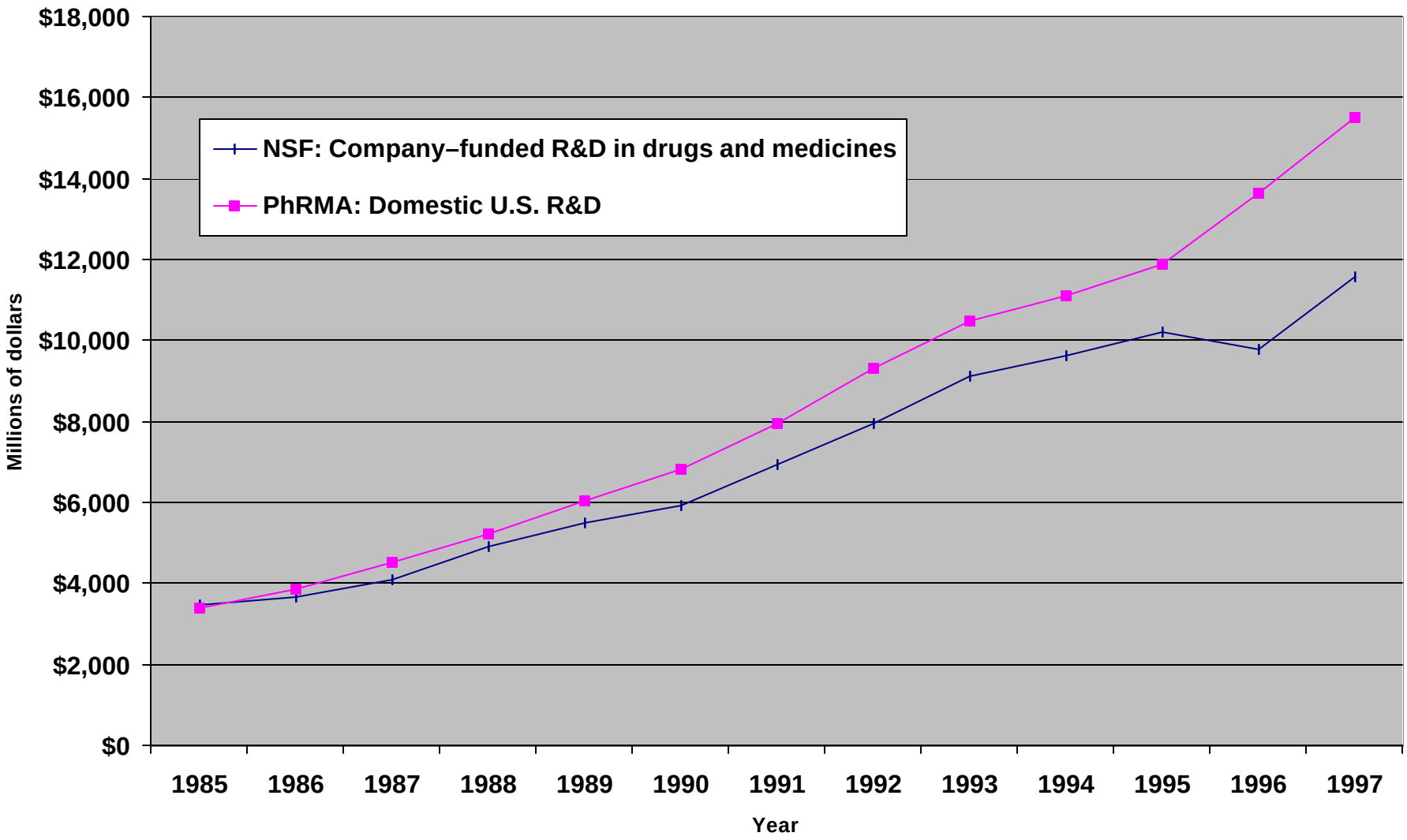


Figure 5
U.S. drug patents granted and total patents granted, 1980 to 2000

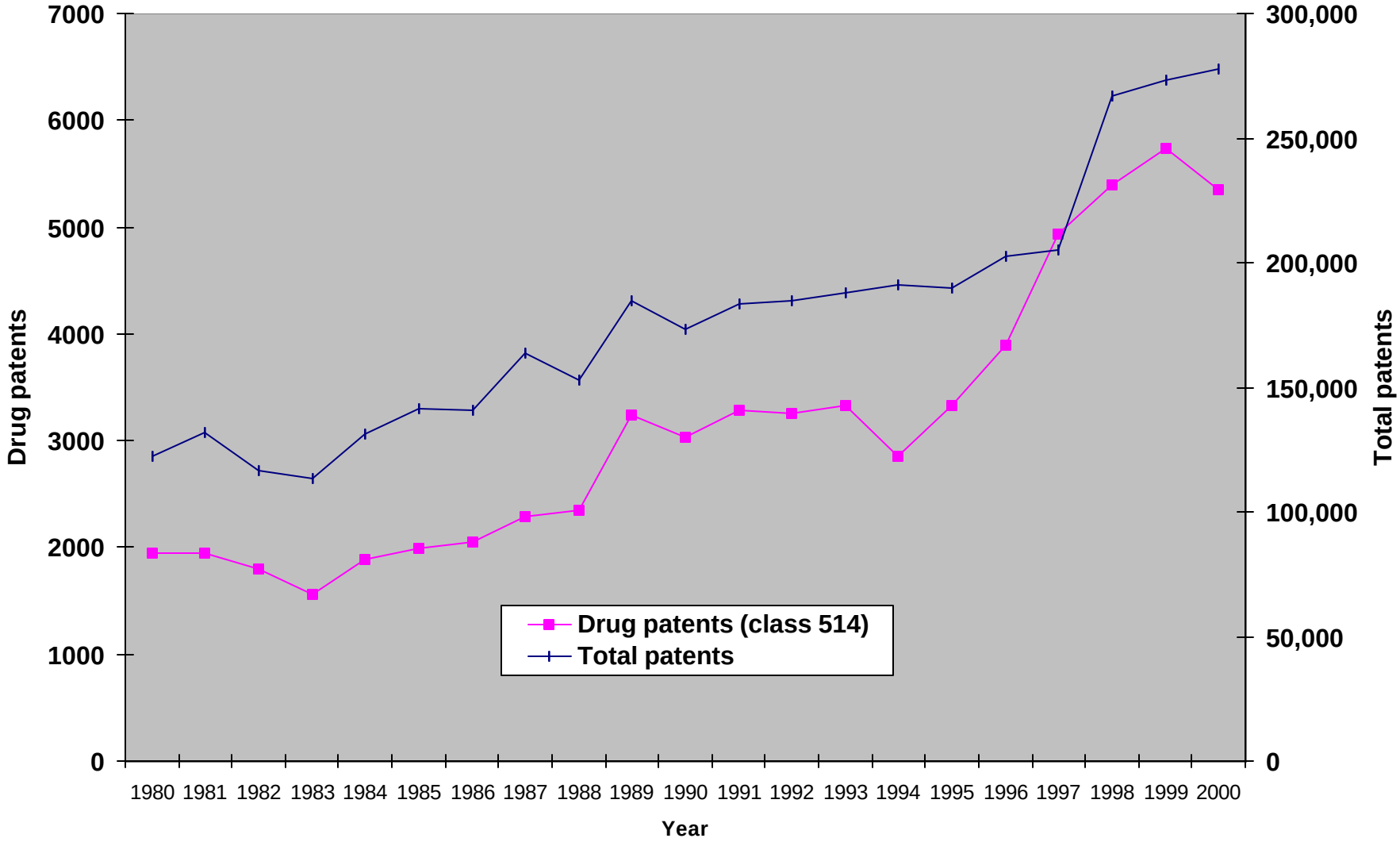


Table 1
Sample data for two indications from NDDF Drug Indications Master Table

ICD9 code	Indication	Drug	Labeled or unlabeled
0119	TUBERCULOSIS	CAPREOMYCIN	L
0119	TUBERCULOSIS	ISONIAZID	L
0119	TUBERCULOSIS	CYCLOSERINE	L
0119	TUBERCULOSIS	ETHAMBUTAL	L
0119	TUBERCULOSIS	ETHIONAMIDE	L
0119	TUBERCULOSIS	AMINOSALICYATE SODIUM	L
0119	TUBERCULOSIS	ACETYLCYSTEINE(INH)	L
0119	TUBERCULOSIS	PYRAZINAMIDE	L
0119	TUBERCULOSIS	RIFAMPIN	L
0119	TUBERCULOSIS	RIFAMPIN AND ISONIAZID	L
0119	TUBERCULOSIS, PULMONARY	RIFAPENTINE	L
272	HYPERCHOLESTEROLEMIA	LOVASTATIN	L
272	HYPERCHOLESTEROLEMIA	PRAVASTATIN	L
272	HYPERCHOLESTEROLEMIA	SIMVASTATIN	L
272	HYPERCHOLESTEROLEMIA	CHOLESTYRAMINE	L
272	HYPERCHOLESTEROLEMIA	COLESTIPOL	L
272	HYPERCHOLESTEROLEMIA	PROBUCOL	L
272	HYPERCHOLESTEROLEMIA	FLUVASTATIN	L
272	HYPERCHOLESTEROLEMIA	ATORVASTATIN	L
272	HYPERCHOLESTEROLEMIA	NIACIN(SA-LIPOTROPIC)	L
272	HYPERCHOLESTEROLEMIA	CERIVASTATIN	L
272	HYPERCHOLESTEROLEMIA	GARLIC	L
272	HYPERCHOLESTEROLEMIA	PSYLLIUM,BRAN	U
272	HYPERCHOLESTEROLEMIA	NEOMYCIN	U
272	HYPERCHOLESTEROLEMIA	CONJ. ESTROGEN,M-PROGESTERONE	U

Table 2

NMEs Approved in Calendar Year 2000

NDA Number	Generic Name	Trade Name	Dosage Form	Applicant	Classification	Approval Date
20-989	Cevimeline HCl	Evoxac	Capsule	Snowbrand	1S	1/11/00
21-014	Oxcarbazepine	Trileptal	Tablet	Novartis Pharms	1S	1/14/00
20-987	Pantoprazole Sodium	Protonix	Tablet	Wyeth Ayerst	1S	2/2/00
21-107	Alosetron HC1	Lotronex	Tablet	Glaxo Wellcome	1P	2/9/00
21-084	Perfluoroalkylpolyether; (PFPE) Polytetrafluoroethylene (PTFE)	Skin Exposure Reduction Paste	Paste	US Army Med Res and Material Command	1,4P	2/17/00
20-789	Zonisamide	Zonegran	Capsule	Elan Pharms	1S	3/27/00
20-971	Articaine HCl 4%; Epinephrine	Septocaine	Injectable	Deproco	1,4S	4/3/00
21-119	Verteporfin	Visudyne	Injectable	QLT PhotoTherapeutics	1P	4/12/00
20-938	Meloxicam	Mobic	Tablet	Boehringer Pharms	1S	4/13/00
21-130	Linezolid	Zyvox	Tablet	Pharmacia and Upjohn	1P	4/18/00
21-081	Insulin Glargine	Lantus	Injectable	Aventis Pharms	1S	4/20/00
20-823	Rivastigmine Tartrate	Exelon	Capsule	Novartis Pharms	1S	4/21/00
21-174	Gemtuzumab Ozogamicin	Mylotarg	Injectable	Wyeth Ayerst	1PV	5/17/00
21-176	Colesevelam HCl	Welchol	Tablet	GelTex	1S	5/26/00
20-986	Insulin Aspart Recombinant	NovoLog	Injectable	Novo Nordisk	1S	6/7/00
20-715	Triptorelin Pamoate	Trelstar Depot	Injectable	Debio Recherche	1S	6/15/00
20-883	Argatroban	Acova	Injectable	Texas Biotech	1S	6/30/00
20-484	Tinzaparin Sodium	Innohep	Injectable	Dupont Pharms	1S	7/14/00
20-610	Balsalazide Disodium`	Colazal	Capsule	Salix Pharms	1S	7/18/00
20-941	Docosanol	Abreva	Cream	Avanir Pharm	1S	7/25/00
21-214	Unoprostone Isopropyl	Rescula	Solution	Ciba Vision	1P	8/3/00
21-197	Cetrorelix Acetate	Cetrotide	Injectable	Asta Medica	1S	8/11/00
21-226	Lopinavir;Ritonavir	Kaletra	Capsule	Abbott Labs	1,4P	9/15/00
21-248	Arsenic Trioxide	Trisenox	Injectable	Cell Therapeutics	1PV	9/25/00
20-687	Mifepristone	Mifeprex	Tablet	Population Council	1P	9/28/00
20-873	Bivalirudin	Angiomax	Injectable	The Medicines Co	1S	12/15/00
21-204	Nateglinide	Starlix	Tablet	Novartis	1S	12/22/00

Figure 6
Number of drugs available to treat condition in year t,
as % of number of drugs available to treat condition in 1979

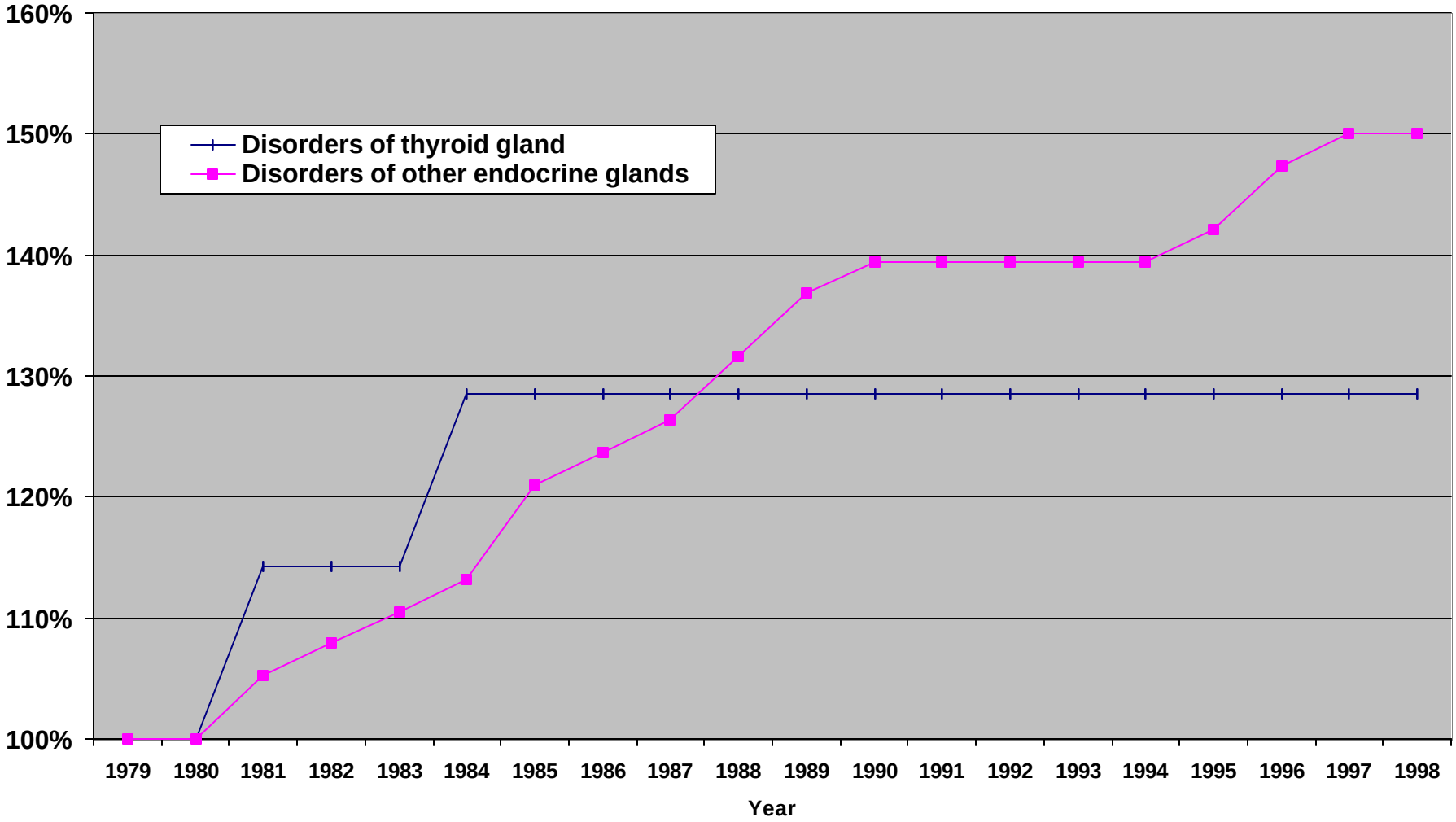


Table 3
Examples of NDA Approvals of New Indications for Existing Drugs

INGREDIENT NAME	CHEMICAL TYPE	APPROVED DATE	THERAPEUTIC CLASS
AMANTADINE HYDROCHLORIDE	NEW MOLECULAR ENTITY	18-Oct-66	ANTIVIRAL - ANTI-INFLUENZA - SYSTEMIC
AMANTADINE HYDROCHLORIDE	NEW INDICATION	18-Apr-73	ANTI-PARKINSON DRUGS
CLOTRIMAZOLE	NEW MOLECULAR ENTITY	3-Feb-75	FUNGICIDES (TOPICAL)
CLOTRIMAZOLE	NEW INDICATION	29-Jul-96	ANTIFUNGAL (CANDIDIASIS)
CROMOLYN SODIUM	NEW MOLECULAR ENTITY	20-Jun-73	BRONCHODILATOR
CROMOLYN SODIUM	NEW INDICATION	3-Jan-97	RESPIRATORY
CYCLOSPORINE	NEW MOLECULAR ENTITY	14-Nov-83	IMMUNOMODULATORS
CYCLOSPORINE	NEW INDICATION	22-May-97	NSAID
CYPROHEPTADINE HYDROCHLORIDE	NEW MOLECULAR ENTITY	17-Oct-61	ANTIHISTAMINE/ORAL
CYPROHEPTADINE HYDROCHLORIDE	NEW INDICATION	18-Sep-69	APPETITE STIMULATION
FLUOXETINE HYDROCHLORIDE	NEW MOLECULAR ENTITY	29-Dec-87	ANTIDEPRESSANTS
FLUOXETINE HYDROCHLORIDE	NEW INDICATION	28-Feb-94	OBSESSIVE COMPULSIVE DISORDER
FLUTICASONE PROPIONATE	NEW MOLECULAR ENTITY	14-Dec-90	STEROIDS
FLUTICASONE PROPIONATE	NEW INDICATION	7-Nov-97	RESPIRATORY
GLYCOPYRROLATE	NEW MOLECULAR ENTITY	11-Aug-61	MISCELLANEOUS UPPER GI DRUGS
GLYCOPYRROLATE	NEW INDICATION	6-Feb-75	ANTICHOLINERGIC AGENT
GOSERELIN ACETATE	NEW MOLECULAR ENTITY	29-Dec-89	GNRH AGONISTS
GOSERELIN ACETATE	NEW INDICATION	18-Dec-95	ANTINEOPLASTIC HORMONES
LANSOPRAZOLE	NEW MOLECULAR ENTITY	10-May-95	PROTON PUMP INHIBITORS
LANSOPRAZOLE	NEW INDICATION	17-Jun-97	SYSTEMIC ANTIBIOTICS--H.PYLORI INDICATION
MEBUTAMATE	NEW MOLECULAR ENTITY	11-Jul-61	ANTI-HYPERTENSIVE AGENTS
MEBUTAMATE	NEW INDICATION	31-Jan-75	SEDATIVES AND HYPNOTICS

Figure 7
Number of Original Medical Device PMAs Reviewed by the FDA, 1981-2001

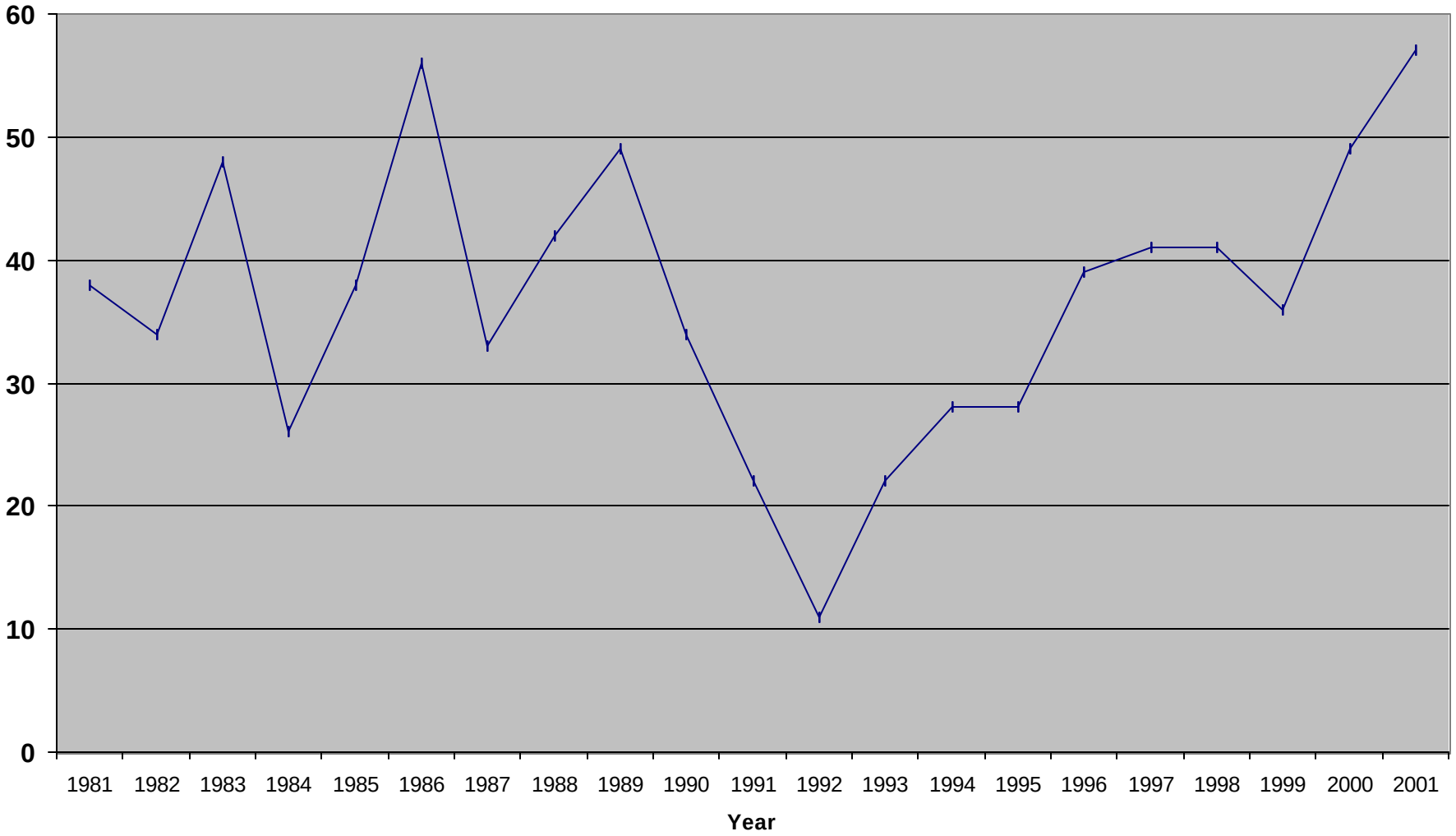


Table 4

Distribution of medical device PMAs reviewed by the FDA, 1981-2001, by Advisory Committee

Number of original PMAs	Cumulative percent of all original PMAs	Advisory committee
338	38%	Ophthalmic
168	57%	Cardiovascular
74	65%	Microbiology
56	71%	General & Plastic Surgery
45	76%	Immunology
32	80%	Gastroenterology & Urology
28	83%	Orthopedic
23	86%	Radiology
22	88%	Obstetrics/Gynecology
18	90%	General Hospital
17	92%	Clinical Chemistry
15	94%	Anesthesiology
12	95%	Ear, Nose, & Throat
12	97%	Dental
10	98%	Physical Medicine
8	99%	Neurology
6	99%	Hematology
6	100%	Clinical Toxicology
1	100%	Pathology

Table 5

Number of deaths, population, and crude death rate, by age group, 1979 and 1998

Year	1979			1998		
Age group	Death Count	Population	Number of deaths per 100,000 population	Death Count	Population	Number of deaths per 100,000 population
1- 4 years	8,108	12,637,000	64	5,251	15,189,749	35
5- 9 years	5,278	16,947,000	31	3,530	19,920,862	18
10-14 years	5,868	18,445,000	32	4,261	19,241,808	22
15-19 years	21,085	21,348,000	99	13,788	19,539,327	71
20-24 years	27,634	21,096,000	131	16,839	17,674,134	95
25-34 years	47,941	36,038,000	133	42,516	38,774,410	110
35-44 years	57,723	25,114,000	230	88,866	44,519,859	200
45-54 years	135,265	22,935,000	590	146,479	34,584,884	424
55-64 years	286,966	21,448,000	1338	233,724	22,675,970	1031
65-74 years	449,255	15,338,000	2929	458,982	18,395,293	2495
75-84 years	493,676	7,598,000	6497	681,663	11,952,189	5703
Over 85 yrs	328,725	2,197,000	14962	612,575	4,053,650	15112
Total	**1,867,524**	**221,141,000**	**844**	**2,308,474**	**266,522,135**	**866**

Source: CDC Compressed Mortality File

Figure 8
Mean age at death vs. life expectancy at birth, 1979-1997

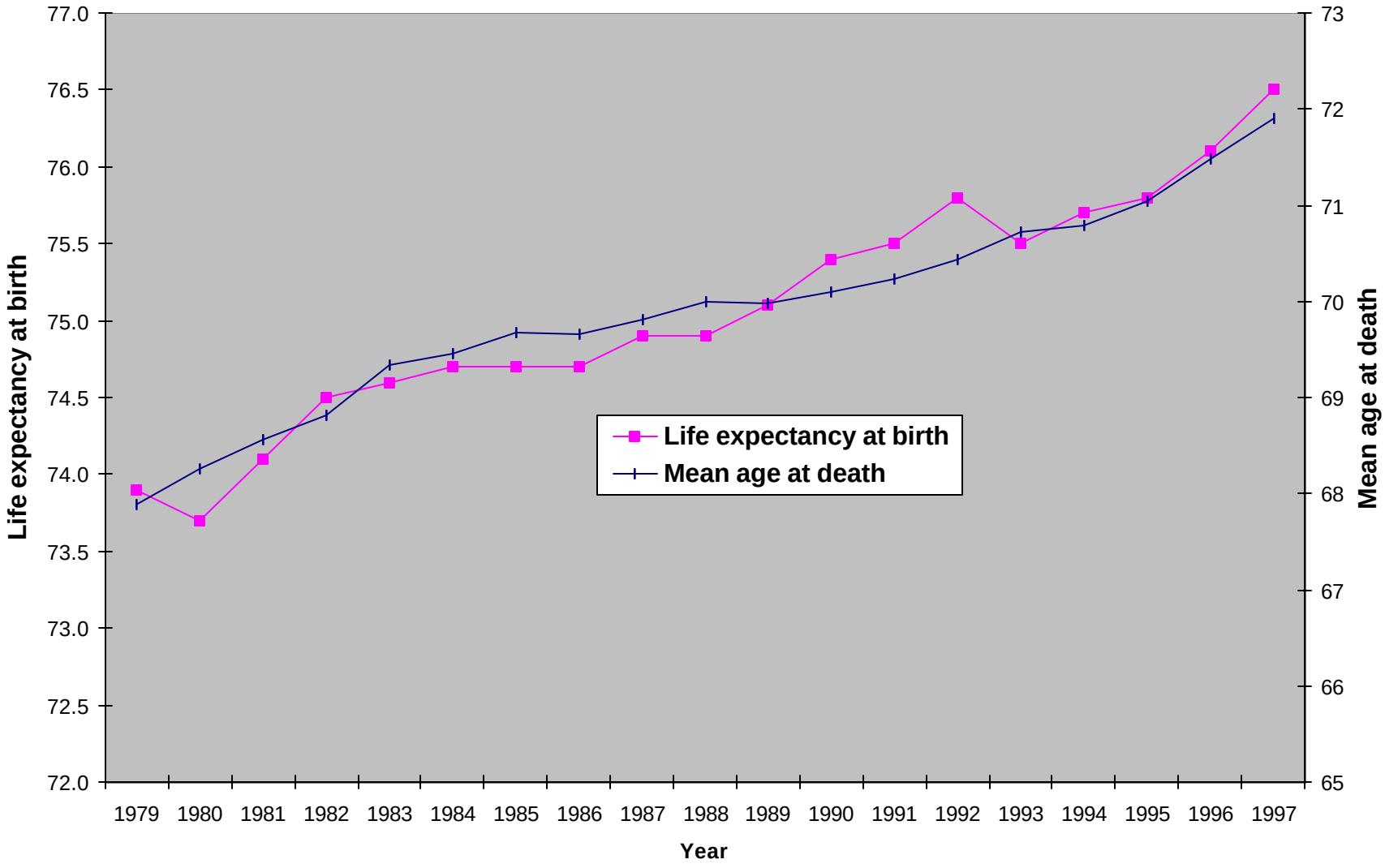


Table 6
Estimates of equations (6) and (7)

Column	1	2	3	4	5	6	7	8	9	10	11	12
Dependent Variable:	Mean age at death	Mean age at death	Fraction dying before age 65	Fraction dying before age 65	Mean age at death	Mean age at death	Fraction dying before age 65	Fraction dying before age 65	Mean age at death	Mean age at death	Fraction dying before age 65	Fraction dying before age 65
Unlabeled indications	excluded	included	excluded	included	excluded	included	excluded	included	excluded	included	excluded	included
DRUG_STOCK	0.01022	0.01268	-0.0001	-0.00029								
	1.58	2.27	0.81	2.66								
	0.1147	0.0232	0.417	0.0079								
PRI_STOCK					0.05324	0.07485	-0.00084	-0.00161	0.04501	0.06493	-0.0006	-0.00142
					2.43	4.01	1.98	4.47	2.51	4.03	1.76	4.56
					0.0152	<.0001	0.0484	<.0001	0.0122	<.0001	0.0794	<.0001
STD_STOCK					-0.00691	-0.00868	0.00019	0.00017				
					0.65	1.05	0.94	1.05				
					0.5129	0.2946	0.349	0.2923				

All equations are estimated via weighted least squares, where the weight is equal to the number of deaths.
All equations include disease and year fixed effects.