

Federal Policies Affecting The Cost And Availability Of New Pharmaceuticals

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Introduction

Prescription drugs¹ are a regular topic of discussion among policy-makers and the media, including their cost, availability, and coverage by insurers. From the availability of AIDS treatments for patients in the developing world, to the potential coverage of pharmaceuticals as an outpatient Medicare benefit, to the manufacture of antibiotics that treat anthrax, the American public and their elected officials in 2002 are grappling with how best to assure that patients have access to the drug therapies they need. The rising cost of prescription drugs is also an issue. In the United States, prescription drug spending doubled between 1995 and 2000 when expenditures reached \$122 billion (Exhibit 1). By comparison, spending for physician and clinical services grew by about one-third, and expenditures for hospitals increased by one-fifth.² Such increases in drug costs contribute to higher insurance premiums for those with drug coverage and higher out-of-pocket spending for those without coverage. Higher costs mean some consumers are less able to afford needed health care. What drives the growing costs of prescription drugs?

The cost of prescription drugs reflects, in part, the scientific talent and long years that go into their discovery and development. Although private industry is largely responsible for the process of bringing new drugs to market, the policies of the federal government affect the costs of and returns to the drug research and development (R&D) process. Some laws, such as those designed to assure the safety and effectiveness of pharmaceuticals, raise the cost of developing and marketing these therapies. Other policies, such as tax deductions and credits designed to encourage some types of drug development, subsidize the process. Patents and other forms of government-granted monopolies make it more attractive for private industry to pursue new drugs, but they also raise their cost for patients and insurers who must pay for drugs. As a result of this close relationship between public policy and private enterprise, pharmaceuticals are often a topic for public debate.

This report identifies several ways in which the federal government influences the availability and cost of prescription drugs and reviews current policy debates surrounding the public's interests in the development and availability of prescription drugs. In particular, it examines:

- intellectual property protection,
- federal support for drug research and development,
- federal tax subsidies,
- and proposals to allow the “reimportation” and resale of drugs sold in foreign countries at prices less than those in the United States.

¹ This paper uses the terms “drugs,” “drug therapies,” and “pharmaceuticals” interchangeably. Unless otherwise noted, these terms refer to pharmaceuticals that require a physician’s (or other qualified medical professional’s) prescription.

²Centers for Medicare and Medicaid Services, Office of the Actuary: National Health Statistics Group. January 2002. <http://hcfa.hhs.gov/stats/NHE-OAct/tables/> .

The federal government's role as regulator and purchaser of prescription drugs, and other issues such as potential outpatient Medicare coverage and the availability of drugs for HIV/AIDS in the developing world, are not addressed in this report.

Pharmaceuticals in the United States: Background

The pharmaceutical R&D enterprise, particularly in the last two decades, has yielded significant benefits for both American health care and the American economy. Drug discoveries in the last twenty years have yielded important new therapies for AIDS, high cholesterol, and depression, among other conditions.³ During the 1990s, a period of significant growth in the U.S. equities, pharmaceutical stocks consistently out-performed the market as a whole. Between 1994 and 2001, median profits across firms averaged 17.2 percent for pharmaceutical manufacturers compared with 13.9 percent for the next most profitable industry, commercial banks, and 4.6 percent for all Fortune 500 firms (Exhibit 2).⁴ Furthermore, the pharmaceutical industry contributed positively to the United States' balance of trade, meaning that exports exceeded imports for pharmaceuticals.⁵

Prescription Drug Spending, Use, and Prices

This profitability reflects, in part, increasing pharmaceutical sales. The increase in prescription drug expenditures during the past several years (mentioned above) mainly reflects change in the number and types of prescription drugs patients use:

- Between 1997 and 2000, increases in the number of prescriptions dispensed contributed 44 percent to the growth in expenditures and changes in the type of drugs used contributed almost 33 percent. Increases in the price of existing drugs contributed the remaining 23 percent.⁶
- Between 1993 and 2000, the number of prescriptions dispensed per capita rose from 7.8 to 10.8, an increase of 38 percent.

At the same time, however, prescription drug prices have risen in recent years significantly faster than prices in the overall economy:

- Between 1991 and 1998, retail prescription drug prices went up at an average annual rate of 7.0 percent, while overall inflation in the economy (the Urban Consumer Price Index or CPI-U) increased by 2.6 percent per year.

³ U.S. Department of Health and Human Services, Office of the Assistant Secretary for Health. *Securing the Benefits of Medical Innovations for Seniors: The Role of Prescriptions Drugs and Drug Coverage*. July 2002, at <http://aspe.hhs.gov/health/reports/medicalinnovation/>.

⁴ Kaiser Family Foundation, Williams, C, Treloar, J, *Trends and Indicators in the Changing Health Care Marketplace, 2002*. (Menlo Park, CA: The Henry J. Kaiser Family Foundation, May 2002), p.46. These estimates represent accounting profits which are one measure of the financial health of private firms commonly examined by stock market investors. Accounting profits can differ significantly from economic profits which measure the return on real economic resources. For a fuller discussion of the differences between accounting and economic profits, see Chapter 3 of U.S. Office of Technology Assessment (OTA), *Pharmaceutical R&D: Costs, Risks and Returns*, (Washington, DC: U.S. Government Printing Office. February 1993).

⁵ Lenz, A. J. and LaFrance, J. *Meeting the Challenge: U.S. Industry Faces the 21st Century. The Chemical Industry*. (Washington, DC: U.S. Department of Commerce. Office of Technology Policy. January 1996). www.ta.doc.gov/Reports/chemicals/chemical.pdf.

⁶ Kaiser Family Foundation, Williams, C. and Treloar, J. *Trends and Indicators in the Changing Health Care Marketplace, 2002*. (Menlo Park, CA: Kaiser Family Foundation. May 2002), p. 45. <http://www.kff.org/content/2002/3161/3161v2.pdf>.

- Between 1998 and 2000, the rate of increase was 9.2 percent per year for retail drug prices compared to 2.8 percent for the CPI.⁷

Insurance Coverage

The financial success of the pharmaceutical industry requires patients who can purchase their products. Without purchasers, there is no revenue. A key to affordability for most patients is health insurance. In 1996, the most recent year for which data are available, 77 percent of the non-elderly population had at least some outpatient prescription drug coverage, and in 1998, 73 percent of the Medicare population had some coverage.⁸ Between 1990 and 2000, third-party reimbursement (i.e., payment by private insurers and Medicaid) increased from 37 percent of retail pharmaceutical sales in the U.S. to 84 percent.⁹ Although there is significant insurance coverage to help provide patients with access to needed therapies and support the health of the pharmaceutical industry, such coverage is far from universal and varies in its generosity. While most workers with employer coverage have drug benefits, increases in employee cost sharing have shifted more of the cost of drugs to workers.¹⁰ As a result, significant pockets of the population are financially vulnerable to pharmaceutical expenses.

New Drugs

The drug industry also needs a research pipeline of new drugs that offer innovation in medical therapies for patients. Both research and development (R&D) investments and the regulation of new drugs have evolved to support the development and marketing of new therapies. U.S. pharmaceutical firms R&D expenditures grew from \$0.6 billion in 1970 to an estimated \$30.3 billion in 2001 (Exhibit 3).¹¹ These expenditures grew at an average annual increase of 12.2 percent between 1995 and 2001, resulting in a doubling of R&D spending over this six-year period. As a percent of sales, R&D has grown over the last three decades from 11.4 percent in 1970 to 17.7 percent estimated for 2001.¹² Furthermore, the number of new drugs approved by the FDA each year has increased somewhat from 20 in 1988 to 24 in 2001. At the same time, however, the number of months necessary for the U.S. Food and Drug Administration

⁷ Kaiser Family Foundation, 2001, *op.cit.*, pp. 28, 30.

⁸Kaiser Family Foundation, 2001, *op. cit.*, p. 15. There is some overlap between the non-elderly population and the Medicare population since the latter group includes about 4 million individuals under age-65 receiving Medicare because they are permanently disabled.

⁹ Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile, 2001*. (Washington, DC: PhRMA. 2001), p. 58.

¹⁰ Kaiser Family Foundation and Health Research and Educational Trust, *Employee Health Benefits: 2001 Annual Survey* (Menlo Park, CA: The Kaiser Family Foundation, and Chicago, IL: Health Research and Educational Trust, 2001). Section 9. Coppock S and Zebrak A, "Statement Before the U.S. Senate Committee on Finance on Finding the Right Fit: Medicare, Prescription Drugs, and Current Coverage Options." Washington, DC: April 24, 2001.

¹¹ Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile, 2002*. (Washington, DC: PhRMA. 2002), p. 75.

¹² PhRMA, 2002, *op. cit.*, p. 76.

(FDA) to approve a new drug application (NDA) fell by almost 50 percent during the same period from 31.3 months to 16.4 months (Exhibit 4).¹³

The R&D process has evolved over the past several decades to reflect changes in biological science. While pharmaceutical research used to depend solely on the random screening of chemical compounds, drug candidates are now “designed” to attack specific molecular features of diseases. Furthermore, biotechnology generally and the mapping of the human genome specifically are expected to expand the number of opportunities for new drug therapies. The faster NDA approval times reflect changes in the FDA mandated by the 1992 Prescription Drug User Fee Act (PDUFA) and the FDA Modernization Act (FDAMA) of 1997, which provided additional resources to the agency through user fees, set a goal of 12 months for the review of new drug applications, and made specific changes in FDA’s procedures to speed up approvals and expand patient access to new drugs. In June 2002, a five-year extension of the user fee program was signed into law as part of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188). However, Congress did not include proposals to extend user fees to generic drugs because of opposition from the generic drug industry who argued such fees would be a disincentive to market generics.¹⁴

Despite new scientific opportunities and a faster regulatory approval process, most newly approved drug products are not necessarily significant therapeutic advances. According to a 2002 analysis by the National Institute for Health Care Management, a growing percentage of newly approved drugs are only incremental modifications of existing drugs. During the period 1995-2000, the report found that the FDA approved 81 percent more incrementally modified drugs that did not offer significant advances in efficacy or safety than it did in the period 1989-1994. By contrast, the number of new molecular entities given priority approval by the FDA because of their therapeutic advances increased only 10 percent during the same period. As discussed later in greater detail in the section on intellectual property protection below, the report cited industry strategies to extend patent protection by making only small changes in existing drugs as the major explanation for the shrinking percentage of new drugs representing significant innovation.¹⁵ Furthermore, some have questioned the validity of estimates of the costs of bringing new drugs to market based on industry-supplied data (See Appendix A).

¹³PhRMA, 2002, op. cit, p. 19. The particularly large drop in average review times between 1993 and 1994 reflects the implementation of the 1992 Prescription Drug User Fee Act, described in the next paragraph.

¹⁴ Congress also dropped a proposal for user fees for medical devices. Democrats opposed the provision because of a clause that would allow groups other than the FDA to review applications for some new devices. *American Health Line*. May 22, 2002 and May 24, 2002. <http://nationaljournal.com/pubs/healthline/m020522> and <http://nationaljournal.com/pubs/healthline/m020524>.

¹⁵ National Institute for Health Care Management Research and Educational Foundation, *Changing Patterns of Pharmaceutical Innovation*. (Washington, DC: National Institute for Health Care Management, 2002). <http://www.nihcm.org/innovations.pdf>.

The Role of the Federal Government and Current Policy Issues

Through law and regulation, the federal government's policies affect the availability of new pharmaceuticals, the cost of bringing them to market, and the returns that drug companies receive for their efforts.

Intellectual Property Protection

At the core of drug firms' decision to develop new therapies is their expected monetary return, which depends in large part on the willingness of the federal government to provide them with the monopoly power of patents. Why are patents necessary? The key asset of any pharmaceutical company is the scientific knowledge underlying its drug products. Unlike the brick and mortar assets of many businesses, there is nothing to keep competitors from using a pharmaceutical firm's scientific discoveries unless the developer successfully keeps the information secret or it receives patent protection from the federal government. Because secrecy is difficult to maintain, firms would have little incentive to take on the costs and risks associated with drug R&D without some period of exclusive marketing that comes with a patent. Issues related to intellectual property protection (i.e., protection through patents and related legal mechanisms to eliminate competition for a defined period of time) and the ability of firms to market their products exclusively have been, and continue to be, a source of federal policy debate.

Generic Competition and Patent Extensions

Patents in the United States are normally granted for 20 years from the date an application is filed with the U.S. Patent and Trademark Office.¹⁶ However, because drug companies usually receive patents early in the drug development process, there are less than 20 years of effective patent life once the drug receives FDA marketing approval. In light of evidence of declining effective patent life, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L. 98-417), also known as the Hatch-Waxman Act. It allowed drug patent holders to receive extensions of up to five years (with the total period between market approval and patent expiration not to exceed 14 years). Other provisions of Hatch-Waxman included:

- a limit of a two-year extension (rather than five years) for those promising drug compounds already in clinical trials or under FDA premarket review;
- a “data exclusivity” or “market exclusivity” that bars generic manufacturers from using brand manufacturers' data in their Abbreviated New Drug Applications (ANDAs) for five years for new compounds and three years for new uses of existing compounds. This latter provision is more likely to provide a significant barrier to

¹⁶ Effective in 1995, P.L. 103-465, the legislation implementing the Uruguay Round trade agreements, made the term of a U.S. patent 20 years from date of application. Prior to this legislation, the federal government issued patents for 17 years from the date they were issued.

entry for new uses of a drug than for new compounds since most brand name manufacturers have more than five years of effective patent life at the time their drugs are approved;

- a standardized and streamlined process for generic drugs to achieve FDA marketing approval by allowing such approval to be based on ANDAs that demonstrated “bioequivalence”¹⁷ between the generic drug and the brand version among other requirements.¹⁸ This last provision created a significant generic drug industry in the United States.¹⁹

Recently both critics and supporters of the drug industry have argued for changes in Hatch-Waxman, although each group seeks different changes. On one side are those who believe the industry needs strengthened exclusivities to assure revenues adequate to justify the costs and risks of new drug R&D. They argue that the law has facilitated entry for generics, giving brand name manufacturers 12 years in which they can recoup their initial research investments.²⁰ However, the same study noted that the patent extensions afforded by Hatch-Waxman actually extended effective patent life by 2.3 years beyond what they would have been without the law.²¹

Industry also points to the emergence in the early 1990s of managed care as having been an impetus to the use of generics. Of drugs that first faced generic competition in 1991 and 1992, generics immediately garnered 20 percent of market share compared with 14 percent during the 1989 and 1990 period. Generics gained 72 percent of market share within 18 months for the drugs first facing competition in 1991 and 1992, compared to 47 percent for the 1989 and 1990 drugs.²² However, data indicates that in recent years, overall generic penetration has not

¹⁷ Bioequivalence refers to the “equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations.” U.S. Department of Health and Human Services, Food and Drug Administration, “The Orange Book Online.” Preface. [http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic Equivalence-Related Terms](http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm#Therapeutic%20Equivalence-Related%20Terms). December 12, 2001.

¹⁸ In addition to being bioequivalent, a generic drug must (1) have the same active ingredient as the innovator drug, (2) have the same indications, strength, dosage form, and means of administration, (3) meet the same requirements for identity, strength, purity, and quality, and (4) be produced according to the FDA’s good manufacturing practice regulations. Strongin, R. J., “Hatch-Waxman, Generics, and Patents: Balancing Prescription Drug Innovation, Competition, and Affordability,” *NPFH Background Paper*. (Washington, DC: The National Health Policy Forum, George Washington, University. June 21, 2002), p. 9.

¹⁹ National Institute for Health Care Management (NICHM) Foundation, *Prescription Drugs and Intellectual Property Protection*. Issue Brief. (Washington, DC: August 2000), pp. 4-5.

²⁰ PhRMA, op. cit, 2001, p. 61.

²¹ Hatch-Waxman appears to have restored the effective patent life for brand name drugs to what they were in the early 1970s before a period of decline. Hunt, M. I., *Prescription Drug Costs: Federal Regulation of the Industry* (Washington, DC: The Blue Cross Blue Shield Association of America. September 2000), Chapter 3. <http://bcbshhealthissues.com/proactive/newsroom/release.vtml?id=17521>.

²² PhRMA, *Pharmaceutical Industry Profile: 2000* (Washington, DC: PhRMA. 2001), pp. 68-70.

been as great as suggested by those earlier numbers. It has stalled at about 42 percent of all prescriptions dispensed and about 18 percent of all prescription drug sales.²³

On the other side are those who believe that current patent exclusivities are sufficient, if not too generous. They point to:

- As shown above in Exhibit 4, significant decreases in the amount of time it takes the FDA to review a new drug application (NDA) in recent years. Lengthening FDA review times were a major impetus behind the original Hatch-Waxman legislation. Average time from submission to approval for new chemical entities (NCEs)²⁴ fell from 2.8 years for NDAs submitted between 1980 and 1989 to 1.8 years for those submitted between 1990 and 1999.²⁵
- Brand name manufacturers often introduce new versions of their drugs with some clinical improvements just prior to patent expiration.²⁶ These new versions carry their own patents and are designed to help maintain market share for the manufacturer of the originator drug. As mentioned earlier, a recent report documents how a growing percentage of newly approved drugs represent only modest changes to existing drugs as opposed to significant therapeutic advances.²⁷ Industry also may engage in “patent stacking” or “evergreening” – i.e., seeking new patents for a new use of a drug or covering how a drug is manufactured.²⁸ Two recent examples of these strategies are the introduction in 2002 of the antihistamine Clarinex by Schering-Plough to replace its earlier drug Claritin for allergies, and the introduction of Nexium in 2001 by AstraZeneca to replace Prilosec for some types of heartburn. In each case, the new drug represents modification of the predecessor’s molecular structure. However, neither firm has scientifically demonstrated that the successor drug is clinically superior to the earlier one.²⁹ AstraZeneca has simultaneously been

²³ Kaiser Family Foundation and Sonderegger Research Center, 2001, *op. cit.*, p. 36.

²⁴ New chemical entities (NCEs) are molecular compounds that have never before been tested or used for therapeutic purposes in humans. OTA, 1993, *op. cit.*, p. 6.

²⁵ DiMasi, J.A., “New Drug Development in the United States,” *Clinical Pharmacology and Therapeutics*. 69 (May 2001) pp. 286-96.

²⁶ Recent examples include a version of Prozac taken once weekly (versus daily for the older version) and an improved version of Prilosec marketed under the name of Nexium.

²⁷ National Institute for Health Care Management, *op. cit.*, 2002.

²⁸ Lilly sought and received a patent for Prozac (approved for marketing by the FDA under the brand name Sarafem) to cover a new use, the treatment of premenstrual dysphoric disorder. This patent does not expire until 2007. Vedantam, S., “Renamed Prozac Fuels Women’s Health Debate.” *Washington Post*. April 29, 2001, p. A1. AstraZeneca also won new “process” patents for Prilosec in its efforts to preserve market share for their version of the drug. “Legislation Introduced to Respond to ‘Patent Stacking’ by Pharmaceuticals.” *BNN Frontrunner*, May 2, 2001.

²⁹ Otto, M.A., “We’re Not Going to Take It: Contrary to Ads’ Message, Clarinex Is Not Better Than Its Predecessor.” *The Washington Post*. March 26, 2002. <http://www.bamcoalition.org/News/HW/03.26.02.htm>.

fighting in court to prevent generic versions of Prilosec from entering the market. Although the drug's primary patent expired in October 2001, AstraZeneca claims in federal district court that a unique method of coating the drug, which is covered by another patent that has not expired, precludes generic competition. The court has not yet ruled on the case.³⁰ Such industry strategies are captured in the data on generic penetration; overall, generic sales represented about 42 percent of retail prescription drug sales between 1996 and 2000. In terms of sales, their share has fallen slightly over the same period from 21 percent to 18 percent.³¹

- Brand name manufacturers engage in other strategies to prevent generic entrants, including filing patent infringement suits and paying generic entrants not to manufacture a drug once they receive FDA approval. In 2001, a proposed consent agreement issued by the Federal Trade Commission (FTC) charged Hoechst Marion Roussel, Inc. and its partner Carderm Capital, L.P. with preventing Andrx Corporation from marketing a generic version of its drug Cardizem CD for the treatment of hypertension and angina pectoris. Hoechst's strategy involved both litigation and a payment to Andrx. Hoechst Marion Roussel settled the case in April 2002.³² In April 2001, the FTC also brought civil charges against Schering-Plough Corporation for allegedly paying two generic manufacturers \$90 million not to market versions of another heart medication K-Dur 20.³³ Under Hatch-Waxman, the FDA is required to implement a 30-month moratorium on generic approvals for a drug if the brand name manufacturer files suit within 45 days of a generic manufacturer's application for marketing approval.
- Legislation adopted over the course of the 1990s has added to the opportunities brand name manufacturers have for additional periods of market exclusivity. This includes the provisions of the American Inventors Protection Act of 1999 (part of P.L. 106-113) that add a day to the term of a patent for each day over three years that it takes the Patent and Trademark Office (PTO) to issue a patent, as well as the pediatric and orphan drug exclusivities discussed in greater detail below. By one estimate,

³⁰ Langreth, R., "Hard To Swallow." *Forbes Magazine*. May 13, 2002.
<http://www.bamcoalition.org/News/HW/05.13.02.htm>.

³¹ Kaiser Family Foundation and Sonderegger Research Center, 2001, *op. cit.*, p. 36.

³² *Federal Register*, vol. 66, p. 18636 (April 10, 2001). "Prescription Drugs: FTC Nominee Says He Would Continue Generic Drug Probe." *Kaiser Network Daily Report*. May 16, 2002.
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=4658.

³³ "McCain Seeking To Move Bill Promoting Generic Drugs." *CQ Monitor News*, May 1, 2001. In July 2002, an administrative law judge dismissed the case against Schering-Plough and Upsher-Smith Laboratories (one of the two generic companies), concluding that the firm did not break any laws. The FTC indicated that it would appeal the judge's decision. The other generic company, ESI Lederle, settled out-of-court with the FTC. Petersen, M., "Schering-Plough Wins Dismissal of F.T.C. Case on Generic Drug," *The New York Times*. July 3, 2002. Kaiser Daily Health Policy Report, "FTC to Appeal Judge's Decision To Dismiss Charges that Schering-Plough Blocked Generic Competition." July 5, 2002 at
http://kaisernetwork.org/daily_reports/print_report.cfm?DR_ID=12064&dr_cat=3.

effective patent life of drugs increased from 8.1 years for drugs approved between 1980 and 1984 to as long as 15.4 years for some drugs approved in the late 1990s.³⁴

Legislation currently being considered by Congress that would alter several key provisions of Hatch-Waxman has garnered significant support among private employers, state governors, and organized labor.³⁵ S. 812, introduced by Senators Charles Schumer (D-NY) and John McCain (R-AZ) *et al.*, and H.R. 1862, introduced by Representative Sherrod Brown (D-OH) *et al.*,

:

- Eliminates the 30-month moratorium against generic approvals when a brand name manufacturer files a patent infringement suit.
- Eliminates the 180-day exclusivity given to the first generic manufacturer that seeks to market a particular drug if the generic manufacturer: does not get FDA approval within 30 months, does not enter the market within 90 days of receiving FDA approval, does not challenge a new patent for the drug's brand version within 30 days, withdraws its marketing application to the FDA, or is determined by the HHS to have "engaged in anti-competitive activities."
- Codifies FDA's methods of determining that a generic drug is "bioequivalent" to its brand-name version, the standard for approving a generic drug.
- Requires the FTC to evaluate the effectiveness of the law within five years.³⁶

Both bills were introduced in May 2001 and referred to committee. While H.R. 1862 awaits action by the House Energy and Commerce Committee, an amended version of S. 812 was reported by the Senate Health, Education, Labor, and Pensions Committee on July 11, 2002 with bipartisan support and awaits floor action expected later in July 2002.³⁷ Under the amended bill:

- Brand name manufacturers would be allowed one 30-month patent extension when filing suit against a generic manufacturer for patent infringement.

³⁴ NICHM Foundation, *op. cit.*, pp. 10-11.

³⁵ Business for Affordable Medicine, "Changes to Hatch-Waxman Drug Law Will Save Billions of Dollars Annually: Governors, Employers, Labor Ask Congress to Eliminate Barriers to Lower-cost Generics." Press Release. (Washington, DC: Business for Affordable Medicine. May 8, 2002). <http://www.bamcoalition.org/Press/5.8.2002PressRelease.pdf>

³⁶ In June 2002, Senator Jay Rockefeller (D-WV) introduced his legislation to reform Hatch-Waxman and to take other measures to improve consumer access to prescription drugs (S. 2677). The bill's most important provisions include: 1) an increase in the federal "match rate" for Medicaid prescription drug costs which has the effect of shifting a greater portion of such costs from the states to the federal government; 2) coverage of all cancer drugs by Medicare (regardless of how they are administered); 3) eligibility for public hospitals to "best prices" for inpatient drugs as determined under the Medicaid drug rebate program; 4) financial penalties for innovator firms who block generic competition by asserting patent claims that are ultimately found to be invalid; and 5) forfeiture of the 180-day exclusivity for generic firms that fail to market an approved generic drug, fail to challenge an innovator's patent claim, fail to win FDA approval within 30 months of filing an ANDA, or are found by the FTC to be engaging in monopolization.

³⁷ All 11 Democrats on the Committee and 5 of the 10 Republicans voted in favor of the amended S. 812.

- The 180-exclusivity for the first approved generic manufacturer would pass to the next manufacturer awaiting FDA approval if the first generic manufacturer does not promptly market the drug. If there is no second generic manufacturer awaiting FDA approval, all potential generic manufacturers would be eligible to seek immediate FDA approval.
- Generic manufacturers could seek injunctions against brand manufacturers who receive new patents for small or inconsequential changes in existing products and try to use the new patents to bar generic competition.
- The reported bill does not codify FDA's method's of determining bioequivalence of generic drugs, and maintains the original bill's requirement that the FTC study the legislation's effectiveness after five years.³⁸

Biological Drugs and Generic Competition

Biological drugs, also referred to as therapeutic biologicals, are pharmaceuticals developed through biological processes rather than the traditional chemical processes that characterize most drugs.³⁹ Another looming issue for the federal government is whether generic versions of therapeutic biologics will be made available to consumers. Drugs are regulated by the FDA's Center for Drug Evaluation and Research (CDER) and are governed by the Food, Drug, and Cosmetic (FDC) Act. Biological materials, on the other hand, come under the jurisdiction of the FDA's Center for Biologics Evaluation and Research (CBER) and the Public Health Service (PHS) Act. In the first years after passage of Hatch-Waxman in 1984, all pharmaceuticals were developed through traditional chemical methods and, hence, regulated by CDER. In the intervening years, however, advances in biotechnology have made possible therapeutic biologics, which are regulated by CBER.

Among the first significant therapies based on biotechnology techniques was Amgen Corporation's Epogen, known generically as recombinant erythropoietin (rEPO), which was approved by the FDA in June 1989 for the treatment of anemia associated with renal failure. A subsequent version of rEPO, marketed as Procrit by Johnson and Johnson's Ortho Biotech division and governed by its own patents,⁴⁰ was approved in 1990.⁴¹

³⁸ Rich, S., "Senate Panel Votes to Boost Drug Competition." *National Journal News Service*. July 11, 2002 at <http://nationaljournal.com/scripts/printpage.cgi?/members/markups/2002/07/200219203.htm>.

³⁹ The FDA defines a biologic as a virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries to humans (21 CFR 600.3h). In essence, they represent organic rather than inorganic material. For the purposes of FDA regulation, biologics include vaccines, blood products, and therapeutic biologics.

⁴⁰ Patents for therapeutic biologics often cover the process for their manufacture, rather than the molecule itself since the molecule is often naturally occurring in humans. For example, the Amgen patent covered the production of rEPO by inserting the human gene for erythropoietin into Chinese hamster ovary cells.

In the intervening years, the number of therapeutic biologics approved by the FDA has increased significantly. While FDA approved five or fewer new biotechnology drugs or vaccines in each of the years 1982-1992, it approved 32 in 2000 and 24 in 2001,⁴² bringing the total number of these products on the market to 199 (Exhibit 5).⁴³

Although Epogen's patents are due to expire by the middle of this decade, the FDA has no ANDA process in place for the approval by CBER of generic versions of therapeutic biologics. Industry maintains that Congress wrote Hatch-Waxman to cover only drugs regulated by the FD&C Act. They further cite a House-passed (but not Senate-passed) resolution (H. Con. Res. 105-196) and the stated intention in 1997 of Senators Jeffords and Kennedy, then Chair and Ranking Member respectively of the committee that oversaw FDA, that Hatch-Waxman not apply to biologics. Furthermore, industry argues that therapeutic biologics rely on trade secrets and non-patent forms of legally protected intellectual property. Generic approvals would require the taking of such property, which industry argues would raise new legal and constitutional questions.⁴⁴ Recently, however, other members of Congress have begun to question whether biologics should be exempt from generic competition.⁴⁵ In 2000, Epogen and Procrit were the drugs with the 7th and 10th highest sales in the United States, together totaling just under \$4 billion in sales. As more therapeutic biologics reach the market and their patents expire, this issue will likely become more important for consumers, insurers, and policy-makers.

Orphan Drugs

Because of the amount of time, money, and risk associated with the development of new drugs, research-based pharmaceutical firms have an incentive to invest in treatments for conditions that affect the largest number of people. The more patients, the more potential revenue, and the more likely the product will recoup its R&D costs. All else being equal, drug companies would be less likely to invest in treatments for diseases that afflict a relatively few people. To address this

⁴¹ U.S. Congress, Office of Technology Assessment, *Recombinant Erythropoietin: Payment Options for Medicare*. OTA-H-451. (Washington, DC: U.S. Government Printing Office. May 1990).

⁴² The number of approvals in any given year (here and in Exhibit 5) includes new drugs as well as new indications for already approved drugs. The 110 total biotechnology products counts a drug with multiple approved indications only once.

⁴³ Biotechnology Industry Organization (BIO), "Biotech Medicines on the Market Top 110 With Hundreds More in the Pipeline." Press Release. (Washington, DC: February 16, 2001). http://www.bio.org/newsroom/newsitem.asp?id=2001_0201_01. Although the numbers presented here and in Exhibit 5 include both biotech drugs and vaccines, the vast majority of products are drugs. For example, of the 32 approvals in 2000, only 2 were for vaccines.

⁴⁴ Lawton, S.E., Vice President and General Counsel, "Letter to Representative Michael Bilirakis, Chairman, Energy and Commerce Committee, Subcommittee on Health, Regarding the Proposed Approval of Generic Biologics." July 26, 2001. <http://www.bio.org/laws/letter072601.html>.

⁴⁵ Bilirakis, M, U.S. Congressman (R-FL), Chairman, Subcommittee on Health, House Committee on Energy and Commerce. Questioning of the Honorable Jane Woodcock, Director, U.S. Food and Drug Administration. Hearing on "Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals." June 13, 2001. <http://energycommerce.house.gov/107/hearings/06132001Hearing276/hearing.htm>.

problem, Congress passed the Orphan Drug Act in 1983 (P.L. 97-414). For conditions that affect fewer than 200,000 people in the United States, or that affect “more than 200,000 in the United States and for which there is no reasonable expectation” that a firm could recover its R&D investment through sales revenue, a firm can apply for orphan drug status. The company can make this request at any time after it has sought approval to test a drug for the condition in humans. More than one firm can receive orphan drug designation for a given condition. Orphan drug designation provides financial incentives for firms to pursue treatments for rare disorders. In particular the law provides for:

- Assistance from the FDA in the design of clinical trials and preparation of marketing applications to the agency;
- Research grants for clinical studies;⁴⁶
- Tax credits equal to 50 percent of a firm’s clinical R&D expenditures (i.e., money spent on studies involving humans) for a potential orphan product (discussed in greater detail later in this brief);
- Seven years of exclusive U.S. marketing rights to the first firm that receives approval to market an orphan drug for a given condition, unless a potential competitor can show that its product provides a “significant therapeutic advantage” over an approved orphan product.⁴⁷

This last provision is particularly strong since it is more binding than a patent exclusivity. It bars competition from any drug for a given orphan condition, not just the particular drug first approved by the FDA. Furthermore, orphan drug status can run beyond the date of patent expiration, depending on how long after patent issuance the manufacturer receives FDA marketing approval. It can also apply to products not covered by any patent at all. As of December 2001, there were 1,142 orphan product designations awarded by the FDA. Of these, 215 had been approved for marketing over the 18-year history of the law (Exhibit 6).⁴⁸

The Orphan Drug law appears to have been successful in bringing new therapies that would not have been otherwise available to patients.⁴⁹ At the same time, however, there have been and continue to be issues and controversies concerning the law: Orphan drug status and exclusivity remain even if the number of affected individuals exceeds 200,000 (as happened with

⁴⁶ Administered by the FDA’s Office of Orphan Products Development, grants support between \$100,000 to \$300,000 in direct costs. For FY 2002, Congress appropriated \$13.2 million for such grants (P.L. 107-76). Although such funding is small given the overall costs of running clinical trials, the FDA identified 27 approved orphan products that had benefited from these grants as of November 2000. <http://www.fda.gov/orphan/grants/faq.htm> and <http://www.fda.gov/orphan/grants/magrants.htm>.

⁴⁷ U.S. Department of Health and Human Services, Food and Drug Administration, “The Orphan Drug Act (as amended)” at <http://www.fda.gov/opacom/laws/orphandg.htm> accessed June 17, 2001.

⁴⁸ <http://www.fda.gov/orphan/designat/index.htm>. December 12, 2001.

⁴⁹ For example, see Levitt J.A., Kelsey, J.V. “The Orphan Drug Regulations and Related Issues.” *Food and Drug Law Journal*. 48 (1993) 525-532, and Shulman, S. R., Bienz-Tadmor B., Seo P.S., at al., “Implementation of the Orphan Drug Act.” *Food and Drug Law Journal*, 47 (1992), pp. 363-403.

AIDS) or if the product is found to be effective against additional conditions.⁵⁰ In the case of AIDS, some have argued that orphan status may not have been necessary once there were more than 200,000 AIDS patients and that the market exclusivity kept prices too high.⁵¹

- Similarly, some argue that drug firms define clinical conditions in an overly narrow manner in order to meet the threshold of affecting fewer than 200,000 patients. Once approved, however, physicians may prescribe the medication to treat a broader spectrum of patients. This strategy is referred to as “salami slicing.”⁵² These situations raise the question of whether the criteria of 200,000 affected individuals is the most appropriate mechanism for identifying treatments that would otherwise not be financially viable.
- After one company receives marketing approval and seven-year exclusivity for its orphan product, potential competitors have an incentive to prove that their product is clinically superior and thus qualified to break the first company’s exclusivity. “Also ran” firms have appealed exclusivity restrictions to the FDA and the courts and have even sought legislative changes that would broaden the circumstances under which competitors could circumvent orphan exclusivities.⁵³ Consumer groups so far have successfully blocked such attempts to change the orphan drug law.

⁵⁰ In the latter case, a potential competitor could seek its own marketing approval from the FDA for treatment of the additional conditions, assuming the drug is not also protected by a patent.

⁵¹ Arno, P.S., Bonuck, K, Davis, M, “Rare Disease, Drug Development and AIDS: The Impact of the Orphan Drug Act. *The Milbank Quarterly*, 73 (1995) pp. 231-243.

⁵² Love, J, “Comments on the Orphan Drug Act and Government Sponsored Monopolies for Marketing Pharmaceutical Drugs.” Testimony before the United States Senate, Committee on the Judiciary, Subcommittee on Antitrust, Monopolies and Business Rights Hearing on the Orphan Drug Act, January 21, 1992. Serial No. J-102-48, pp. 259-283. <http://www.cptech.org/ip/health/orphan/orphan92.html>. When the Orphan Drug Law was first passed, designations and exclusivities were to be based on an analytic determination by the FDA that these federal guarantees were necessary for the sponsoring firm to recoup its R&D investments. In the face of FDA difficulties in implementing this provision, however, Congress amended the law to adopt the 200,000 standard in 1994.

⁵³ For example, after Biogen received marketing approval in 1999 for Avonex, a beta-interferon treatment for multiple sclerosis that has orphan designation, Serono attempted to convince the FDA that it should be able to market Rebif, its own treatment for multiple sclerosis. It argued that Serono’s exclusivity should apply only to its method of administration, which was how Serono proved its product was safer and thus clinically superior to an earlier version. After unsuccessfully trying to convince the FDA to lift Biogen’s exclusivity and to convince Congress to change the orphan drug law itself, Serono conducted new clinical studies to demonstrate Rebif’s clinical superiority. Interpretation of the results of that study subsequently became the subject of a lawsuit. Aoki, N, “The Price of Success: Orphan Drug Act Has Spurred Advances – And Disputes.” *The Boston Globe*. July 25, 2001, p. F1.

In the 107th Congress, several pieces of legislation concerning the orphan drug program have been introduced,⁵⁴ but only one has progressed beyond its assigned committee. S. 1379, introduced by Senators Edward Kennedy (D-MA) and Orrin Hatch (R-UT) and reported by the Committee on Health, Education, Labor, and Pensions on December 18, 2001 (Senate Report 107-129), would authorize additional funding and support for the grants program and provide statutory authority for the National Institute of Health's Office of Rare Diseases.⁵⁵ It would not address any of the exclusivity issues outlined above.

Pediatric Exclusivity

In an effort to encourage drug manufacturers to study the effect of new pharmaceuticals on children, the Food and Drug Administration Modernization Act (FDAMA) of 1997 (P.L. 105-115) directed the FDA to give six additional months of market exclusivity beyond any governing patents or other exclusivities to companies that perform pediatric studies approved by the FDA. As of October 2001, the FDA received 275 proposed pediatric study requests from which the agency invited 202 actual studies. From the time the law went into effect in February 1998 through May 2002, FDA had granted 57 exclusivities to 54 different drugs (one manufacturer received two 6-month periods of exclusivity for the same drug, while two drugs resulted in two exclusivity periods each granted to different manufacturers). An analysis submitted to Congress in January 2001 concluded that the provision had substantially increased understanding of pharmaceuticals' effects on pediatric populations with some continuing difficulties in promoting research on antibiotics, products with low sales (where the value of the exclusivity is minimal), and the very, very young.⁵⁶

Although the original pediatric exclusivity expired on January 1, 2001, the Best Pharmaceuticals for Children Act (P.L. 107-109, sponsored in the House by Representative James Greenwood, R-PA, and in the Senate by Senators Christopher Dodd, D-CT and Michael DeWine, R-OH) became law on January 4, 2002 and extended the exclusivity through October 1, 2007. This legislation also modified the original law by making drugs with no current, binding patent or exclusivity eligible for a pediatric exclusivity, by including funding and incentives for clinical, and by setting a timetable for pediatric labeling of pharmaceuticals studied in the pediatric population.

⁵⁴ In particular, H.R. 386, which would clarify the circumstances under which a drug shown to be clinically superior to an existing orphan drug may be approved during the seven-year period of exclusivity, H.R. 4014, which would authorize up to \$25 million for the orphan drug grants program, and S. 1341, which would expand the definition of clinical trials qualifying for the orphan drug tax credit.

⁵⁵ A companion bill, H.R. 4013, was introduced in the House by Representative John Shimkus (R-IL) et al. on March 20, 2002 and reported by the House Energy and Commerce Committee on June 26, 2002 (House Report 107-543).

⁵⁶ <http://www.fda.gov/cder/pediatric>, May 22, 2002. U.S. Department of Health and Human Services, Food and Drug Administration. *The Pediatric Exclusivity Provision--January 2001 Status Report to Congress*. Washington, DC. January 2001.

Although these bills passed with broad bipartisan support,⁵⁷ some, including Representative Henry Waxman (D-CA), a sponsor of the original 1997 legislation, have questioned whether the pediatric exclusivity represents an excessive public subsidy. In particular, they note that clinical trials for children average \$200,000 to \$3 million, while the added revenue to the firm attributable to the exclusivity can be 100 times that amount.⁵⁸ Attempts to modify the legislation in committee to curtail the exclusivity whose prices are deemed excessive failed.

Bioterrorism, HIV/AIDS, and Intellectual Property Protection

Two recent policy issues have called into question the limits of patent protection – the threats posed by anthrax in the United States and HIV/AIDS in the developing world. Federal law gives the government the right to a compulsory license to patents when patented goods are to be manufactured by or for the government itself (28 USC 1498). However, the federal government exercises this right at the risk of creating disincentives to innovation.

The discovery of anthrax in October 2001 among Congressional staff, media personnel, postal workers and others as the result of several tainted letters created a need for sufficient quantities of antibiotics to treat the disease and prevent illness among those exposed. Ciprofloxacin, also known by its brand name Cipro, is a drug with an FDA-approved indication for the treatment of anthrax.⁵⁹ The federal government sought to stockpile 1.2 billion pills. Concern over the potential for profiteering by Bayer, which holds a patent on ciprofloxacin, led the Secretary of DHHS to seek Congressional approval to break Bayer's patent. In the end, the company agreed to lower its price from \$1.77 a pill to \$0.95 for the first 100 million, \$0.85 for the next 100 million, and \$0.75 for the remainder.⁶⁰

In the case of HIV/AIDS, several developing and developed nations have threatened in recent years to break patents on antiretroviral therapies in order to manufacture and provide them at more affordable costs. Although these are not actions by the U.S. government, it does become an issue for the federal government since current U.S. foreign policy seeks to aid other nations battling HIV/AIDS.

⁵⁷ The bill passed the House by a voice vote of 338-86 and the Senate without amendment by unanimous consent.

⁵⁸ Congressman Waxman cited one heartburn drug whose pediatric studies cost \$2 to \$4 million, but whose exclusivity was valued at \$1.2 billion. The FDA's report made some more general conclusions about who pays for the exclusivity. FDA estimated that the pediatric exclusivity would add one half of one percent to the nation's pharmaceutical spending with the government paying about one fifth of that amount through Medicaid and other public programs. According to the FDA study, lower income families without health insurance in need of the affected drugs bear a disproportionate share of the burden, while the generic industry would forego an average \$537 million a year, or about 7 percent of its annual sales. Peterson, M.M., "Drug Companies Get Renewed Patent Protection for Pediatric Testing." *National Journal Online*. October 4, 2001. <http://nationaljournal.com/members/markups/2001/10/200127711.htm>. U.S. DHHS, FDA, *op. cit.*, pp. 15-17.

⁵⁹ Although ciprofloxacin is the only drug specifically approved by the FDA to treat anthrax, research has shown other antibiotics to be effective against the disease.

⁶⁰ Wayne L, Petersen M, "A Muscular Lobby Tries to Shape Nation's Bioterror Plan." *The New York Times on the Web*. November 4, 2001. www.nytimes.com. Nader R, Love J, "Letter to DHHS Secretary Tommy Thompson." October 18, 2001. <http://www.cptech.org/ip/health/cl/cipro/nadethom10182001.html>.

While an analytic debate has occurred over the importance of patients in preventing access to antiretroviral therapies in poorer countries,⁶¹ a coalition of drug companies has agreed to provide their HIV drugs at no-cost or substantially-reduced costs to several countries, thus putting off this question of what limits the federal government would place on patent monopolies in the interest of public health.

Federal Support for Drug Research and Development

The federal government subsidizes the drug R&D process through the work of federal laboratories, most notably the National Institutes of Health (NIH).⁶² Of the \$56.4 billion spent on health R&D in the United States in FY 1999, NIH expenditures constituted 28 percent, with industry responsible for another 60 percent (Exhibit 7).⁶³ However, total appropriations for NIH have grown rapidly in recent years. Between FY 1990 and FY 2002, NIH spending more than tripled, rising to \$23.6 billion in FY 2002 (Exhibit 8).⁶⁴ Much of this growth has been in the past few years as part of a conscious policy by the congressional appropriations committees to double NIH appropriations between FY 1998 and FY 2003.⁶⁵ How do NIH expenditures subsidize the drug R&D process?

Training Support

The most valuable asset of the pharmaceutical industry is its intellectual property and the scientists who create it. PhRMA has reported that in 1999 its member companies (i.e., pharmaceutical firms currently marketing brand name drugs in the United States) employed 14,703 Ph.D. scientists and 3,056 M.D.s in its domestic R&D operations.⁶⁶ For almost 30 years, the federal government has supported the training of biomedical scientists in the United States,

⁶¹ See Attaran A, Gillespie-White L, "Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa." *JAMA*. Consumer Project on Technology, "Comment on the Attaran/Gillespie-White and PhRMA Surveys on Patents on Antiretroviral Drugs in Africa." October 16, 2001. <http://www.cptech.org/ip/health/africa/dopatentsmatterinafrica.html> .

⁶² Although this brief focuses on the largest provider of federal biomedical research support, the National Institutes of Health, other parts of the federal government (including other agencies of DHHS as well as the Departments of Energy and Defense) also fund work that may be directly or indirectly relevant to the drug R&D process.

⁶³ Research! America, *How Much Is Really Spent on Medical & Health Research?* Issue Brief. <http://www.researchamerica.org/media/briefs/spent.html> . December 12, 2001.

⁶⁴ This paper discusses NIH budget data rather than NIH research expenditures because (1) the former is readily available, and (2) the two figures are almost the same. In FY 2002, 92 percent of the NIH budget was for direct or indirect research expenditures. Those items that one could argue are not related to research (training, cancer control initiatives, construction, the Office of the Director, and the National Library of Medicine) constitute only \$1.8 million or 8 percent of the total. <http://www4.od.nih.gov/officeofbudget/CJ2003/Obl.%20Hist.%20by%20Mech.PDF>, accessed May 23, 2002.

⁶⁵ "Committee Files FY00 Spending Bill for Labor, Health, and Education Programs." Press Release. House Appropriations Committee. Washington, DC. October 25, 1999. http://www.house.gov/appropriations/new/106_1pr001acf.html .

⁶⁶ PhRMA, *Pharmaceutical Industry Profile, 2001*, (Washington, DC: PhRMA, 2001), Table 20, p. 135.

including those who work in industry, through NIH-administered National Research Service Awards (NRSA) and a few other smaller programs. In FY 2000, NIH provided NRSA to 16,164 pre-doctoral and post-doctoral trainees at a cost of \$592 million (or 3 percent of the NIH budget).⁶⁷ Biomedical research trainees also receive federal support by working as research assistants on their professors' NIH-funded research grants. In FY 2001, the federal government devoted 58 percent of the NIH budget (or \$11.7 billion) to extramural research projects and grants, all of which went to universities or other non-profit research institutions.⁶⁸

Research Support

NIH-funded research also directly or indirectly results in new pharmaceuticals. In a few cases, the contribution is clear and direct. For example, the drug Ceredase, the first approved therapy for Gaucher disease, was discovered in a laboratory at NIH itself and developed by the biotechnology firm Genzyme.⁶⁹ Through the 1980s, the development of drugs for some conditions including cancer and AIDS was the result of close collaboration between NIH and the drug industry with clear federal investments in testing potential pharmaceuticals both in the laboratory and in patients.⁷⁰ In other cases, it is more difficult to draw a direct line from federal research spending to a particular drug:

- As noted above, the bulk of all NIH research dollars support projects carried out by scientists in universities and other organizations. As a recent NIH report pointed out, there is no on-going system to track what federally-supported extramural research has resulted in a drug product or their associated patents.⁷¹

⁶⁷ Congress established the NRSA program in 1974 (P.L. 93-348). NIH provides NRSA funds to universities that in turn provide them to individual awardees. Pre-doctoral trainees can receive up to five years of support including a stipend of \$16,500 per year. Post-doctoral trainees can receive up to three years of support with a stipend of between \$28,260 and \$44,412 depending on their level of experience. NRSA awardees must “payback” one month of biomedical research (in an academic, nonprofit, or industrial setting) for each month of training support they receive.

⁶⁸ NIH budget data from <http://www.nih.gov/news/BudgetFY2002/FY2001investments.htm#fundingresearch>. A recent National Science Foundation report indicated that 28 percent of graduate students in the life sciences reported that such research assistantships represented their primary means of support. Other students reported their primary support came from fellowships (8 percent), traineeships such as NRSA (10 percent), teaching assistantships (13 percent), self-support (35 percent), and other sources (6 percent). National Science Board, *Science and Engineering Indicators 2000* (Arlington, VA: National Science Foundation. 2000), Appendix Table 6-36.

⁶⁹ Garber, A.M., Clarke A. E., Goldman D. P., et al., “Federal and Private Roles in the Development and Provision of Alglucerase Therapy for Gaucher Disease.” Background Paper for the U.S. Congress, Office of Technology Assessment, OTA-BP-H-104. (Washington, DC: U.S. Government Printing Office. October 1992).

⁷⁰ U.S. Congress, Office of Technology Assessment. *Pharmaceutical R&D: Costs, Risks, and Rewards*. OTA-H-522. (Washington, DC: U.S. Government Printing Office. February 1993). Chapter 9.

⁷¹ As described below, a 2001 NIH report did include a one-time analysis whether NIH contributed to the development of FDA-approved drugs with sales in excess of \$500 million per year. U.S. Department of Health and Human Services, National Institutes of Health, “A Plan to Ensure Taxpayers’ Interests Are Protected: NIH Response to the Conference Report Request for a Plan to Ensure Taxpayers’ Interests are Protected. (Bethesda, MD: National Institutes of Health). July 2001. <http://www.nih.gov/news/070101wyden.htm> .

- Much of NIH-supported research is “basic” in nature – i.e., investigation to gain better understanding of fundamental disease processes or other topics without specific applications in mind. Although such work is done without thought to specific, potential drug therapies, it may have some indirect bearing on eventual pharmaceuticals. The National Science Foundation (NSF) characterized over half (54 percent) of all federal health R&D spending in FY 2000 as basic, with the remainder being applied research or development.⁷²
- Some NIH-funded work may lead to biological materials or laboratory processes that make it possible to pursue R&D directly relevant to new pharmaceuticals. For example, the development of recombinant techniques in the 1970s and 1980s made possible biotechnology drugs starting with Epogen. However, such materials and techniques may not be specific to one or more drug products.

These measurement difficulties notwithstanding, the mission of NIH is “to uncover new knowledge that will lead to better health for everyone” – i.e., it is focused on applying knowledge. Since pharmaceuticals are a significant and growing means of trying to improve health, it stands to reason that a substantial part of NIH’s research portfolio would be directly or indirectly related to drug R&D. Although there have been no recent estimates of how much NIH spends on drug R&D, one study by the Congressional Office of Technology Assessment estimated that in 1988, NIH and ADAMHA (whose laboratories are now part of NIH)⁷³ spent about \$400 million on pre-clinical drug discovery, or 14 cents for every \$1.00 spent by industry on pre-clinical⁷⁴ R&D. The same study also estimated that these federal agencies spent about \$200 billion on clinical drug R&D, or 11 cents for every \$1.00 spent by industry of clinical drug R&D.⁷⁵

⁷² National Science Board, *op. cit.*, 2000. Chapter 2. According to NSF, “applied research is aimed at gaining the knowledge or understanding to meet a specific, recognized need. In industry, applied research includes investigation oriented to discovering new scientific knowledge that has specific commercial objective with respect to products, process, or services. Development is the systematic use of the knowledge or understanding gained from research directed toward the production of useful materials, devices, systems or methods, inducing the design and develop of prototypes and processes.” For pharmaceuticals, development refers to formulation of a drug product and its laboratory and clinical testing.

⁷³ ADAMHA was the Alcohol, Drug Abuse, and Mental Health Administration. In 1992, P.L. 102-321 moved the research aspects of the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Mental Health out of ADAMHA to NIH. The remaining parts of ADAMHA became the Substance Abuse and Mental Health Services Administration (SAMHSA).

⁷⁴ “Clinical research” refers to the testing of potential pharmaceutical compounds in humans for effectiveness and/or safety. “Pre-clinical research” refers to all work done on a potential pharmaceutical prior to testing it humans. This includes initial synthesis of the compound and testing of it in the laboratory and in animals. PhRMA, *op. cit.*, 2001, p. 137.

⁷⁵ OTA, 1993, *op.cit.*, pp. 213-215.

Recent studies have further documented the intimate role that federally-funded research plays in the development of new drug therapies:

- The 2001 NIH report mentioned above found that of the 47 FDA-approved drugs that had sales of at least \$500 million per year, four were developed in part with technologies created in federal laboratories.⁷⁶
- In 1996, an official of the National Cancer Institute (NCI), a part of the NIH, claimed that his institution played an important role in the R&D of 52 out of 77 cancer drugs approved by the FDA.⁷⁷
- In 1998, reporting by the *Boston Globe* found that funds from the NIH or FDA were used in the R&D of 45 out of 50 top-selling drugs approved by the FDA between 1992 and 1997.
- Another study of 30 drugs approved between 1987 and 1991 and deemed by the FDA to be significant therapeutic advances found that 15 had federal involvement in their research at some stage, and 11 had federal involvement in every stage (initial discovery, pre-clinical testing, and clinical testing).
- An analysis of 15 “important” drugs approved between 1970 and 1995 found the significant scientific research that enabled 11 of these therapies was publicly funded.
- Other studies of pharmaceutical patents document drug firms’ extensive citation of publicly-funded and/or publicly carried out research in their patent applications.⁷⁸

Protecting the Public’s Research Investment

The significant federal investment in research that directly or indirectly contributes to new pharmaceuticals has raised concern about the reasonableness of prices charged for such products. The argument made by some is that a drug’s price should reflect any public investment in its R&D. And because the federal government is a purchaser of drugs through programs such as Medicaid, Medicare, health insurance for military and civilian government personnel, and the Department of Veterans Affairs, the taxpayer could end up paying twice – once through its initial research funding and then again through the programs just mentioned.

Pricing of products developed with public funds has generated the most concern for drugs discovered or at least partially developed in federal laboratories such as the National Institutes of Health. From the late 1970s through the 1980s, Congress enacted laws designed promote the practical application and commercialization of intellectual property produced with federal

⁷⁶ NIH, *op. cit.*, 2001.

⁷⁷ A 2002 editorial claims that by 1997, 54 of the 84 FDA-approved drugs for cancer had been developed with federal funding. Arno P. and Davis M, “Paying Twice for the Same Drug.” *The Washington Post*. March 27, 2002. p. A21. <http://www.washingtonpost.com/ac2/wp-dyn/A22829-2002Mar26?language=printer> .

⁷⁸ All studies mentioned in this bulleted list (except the NIH study in the first bullet) are summarized in Hunt, *op. cit.*, 2000, Chapter 2.

funds.⁷⁹ Congress took these actions in recognition of the potential of inventions from federal laboratories to benefit the public health. However, Congress also realized that the federal government had neither the skills nor the practical ability to commercialize such inventions itself. Among other provisions, these laws give universities and nonprofit organizations patenting rights for intellectual property produced through federal grants to those institutions. They also direct federal laboratories to promote the commercialization of their own research, especially through patenting and licensing. A license is a contract to allow the use of a patented technology by an organization or person who does not hold the patent.

While the number of patents issued to and licenses executed by NIH has generally gone up over the 1990s, there has been year-to-year variation (Exhibit 9). Of the 185 licenses executed in FY 2000, 84 percent were non-exclusive, meaning that more than one company or organization can license the same patent. NIH reports that the bulk of these licenses were for diagnostic and research tools. The other 16 percent were exclusive licenses, which means no other entity could license the technology for the same purpose. The majority of these licenses are for drug and vaccine technologies.⁸⁰ These licenses have generated an increasing stream of revenue which is shared between inventing NIH scientists and the institute within which they work (Exhibit 10).

Although NIH policy prefers non-exclusive licensing of its technologies, the agency does allow them for certain patents including those that grow out of Cooperative Research and Development Agreements (CRADAs).⁸¹ In 1989, NIH instituted a policy that there should be “reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public” and applied it to all exclusive licenses emanating from CRADAs.⁸² Subsequent NIH-convened panels representing government, academia, industry, and patients concluded:

- that the primary goals of public research investment and federal technology transfer policy should foster scientific discoveries and their rapid development into medical applications.

⁷⁹ The Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480); the Patent and Trademark Amendments of 1980, known as the Bayh-Dole Act (P.L.96-517); and the Federal Technology Transfer Act of 1986, or FTTA (P.L.99-502).

⁸⁰ NIH, *op. cit.*, July 2001, Appendix A-3.3.

⁸¹ CRADAs, authorized by the FTTA, are formal research partnerships between federal laboratories such as NIH and private partners. The federal laboratory provides resources other than money to the collaboration. The private partner provides both intellectual resources and funding.

⁸² NIH never specified criteria or quantified exactly what constituted this “reasonable relationship.” However, it did require manufacturers subject to this policy to provide “reasonable evidence” to justify the price of their products. Among the handful of cases in which NIH implemented this clause was the drug ddI manufactured through an exclusive license given by the federal government to Bristol-Myer Squibb. NIH held a public hearing in 1992 at which representatives of patient groups voiced no objections to the drug’s proposed price or Bristol-Myer Squibb’s plan to give the drug free to individuals who could not otherwise afford it. OTA, *op. cit.*, 1993, pp. 221-222.

The panel ranked patient accessibility to those products and licensing revenues to the taxpayer as less important, and

- that the reasonable pricing clause presented a significant barrier to accomplishing that goal.

In 1995, the NIH Director eliminated the reasonable pricing policy in reaction to the decision by many firms to end their collaborations with NIH.⁸³

In response to a Congressional mandate first proposed by Senator Ron Wyden (D-OR), NIH released a report in July 2001 (mentioned earlier) that identified four drugs with sales in excess of \$500 million a year that received NIH funding and presented a “plan to ensure that taxpayers’ interests are protected.”⁸⁴ In the report, NIH reiterated its conclusion that a reasonable pricing clause would inhibit technology transfer and the development of new health care products.⁸⁵

However, the report also highlighted the difficulty in identifying NIH funding that may have contributed to the development of new products.⁸⁶ Among the steps NIH plans to take: it will require extramural grantees to report to NIH any newly marketed product that makes use of NIH-funded technology, and NIH will make that information available in a web-based database.⁸⁷

The House of Representatives has seen the reasonable pricing clause differently. In both the FY 2001 and FY 2002 Labor/HHS Appropriations bills, the House legislation reinstated the reasonable pricing policy. However, the measure failed each time in the Senate. Some outside experts have also argued that the Bayh-Dole Act contains an implicit obligation for an enforceable reasonable pricing clause.⁸⁸ Senator Wyden, chair of the Senate Subcommittee on Science, Technology, and Space, has indicated his intention to hold hearings on the NIH report and its underlying issues, although as of May 2002 he has not yet convened this hearing.⁸⁹

⁸³ Although there is no evidence of how the elimination of the reasonable pricing clause has affected patient financial access to drugs developed with federal money, the action did seem to make collaborative research with NIH more attractive to private industry. Between 1995 and 1997, the number of new CRADAs executed jumped 378 percent, from 32 to 153. NIH, *op. cit.*, July 2001.

⁸⁴ Conference report (H. Rept. 106-1033) accompanying the FY 2001 Departments of Labor and Health and Human Services Appropriations Bill, H.R. 4577.

⁸⁵ Instead, NIH indicated it would convene a new group of relevant experts “to establish a thoughtful dialogue on the appropriate returns to the public” for products developed with taxpayer support.

⁸⁶ The Congressional Office of Technology Assessment highlighted this same problem in its 1993 report on the economics of the drug R&D process. OTA, *op. cit.*, 1993, pp. 201-235.

⁸⁷ As of May 2002, only intramurally-developed technologies available for licensing are listed through the NIH Office of Technology Transfer web site. <http://ott.od.nih.gov/index.html>.

⁸⁸ Arno and Davis, *op.cit.*, 2002.

⁸⁹ “Sanders Passes Prescription Drug ‘Reasonable Pricing’ Amendment.” Press Release, Office of the Honorable Bernie Sanders, U.S. House of Representatives. October 10, 2001.

In considering the appropriate policies to govern federal research that contributes to new pharmaceuticals or other health care products, two fundamental questions remain:

- What is the appropriate balance between promoting innovation and assuring patient access to those innovations?
- If one were to mandate that prices reflect federal investments in a drug's R&D, how would one identify that investment and determine an appropriate price?

Federal Tax Subsidies

The federal taxpayer also supports the pharmaceutical R&D process (as it does most of the country's private enterprise system) through federal tax policies. The most important of these subsidies are several tax credits which are subtracted directly from the amount of tax a firm would otherwise pay:⁹⁰

The Research and Experimentation (R&E) Tax Credit

The Economic Recovery Act of 1981 created a new tax credit to encourage firms to increase the amount they spend on R&D from year to year. Congress has extended the tax credit ten times since its enactment and has made some changes that have had the effect of somewhat reducing the benefit to taxpaying firms. Three of these renewals occurred retroactively after the credit had expired, and for a year in 1995-1996, there was no credit at all. In general, the credit is 20 percent of the difference between R&D spending in the current year and the average R&D expenditure over the previous three years, or 50 percent of current year expenditures, whichever is greater.

The R&E tax credit covers all R&D necessary to obtain FDA approval to market a drug in the United States. Although no estimates exist for the total value of the credit taken specifically by the pharmaceutical industry, the steady increases in R&D spending in recent years by drug firms suggests they have been a significant beneficiary of this credit. According to estimates from the Office of Management and Budget, the R&E tax credit cost the Treasury between \$1.2 and \$3.3 billion a year between FY 1995 and FY 1999.⁹¹

The current credit was reauthorized in 1999 for a five-year period ending on June 30, 2004. The pharmaceutical industry, among others, has long sought to make the credit

<http://bernie.house.gov/documents/releases/20011012115004.asp>. Shadid, A, "A US Share of Royalties on Research Is Opposed." *The Boston Globe*. August 22, 2001, p. A1. "Wyden Calls On Congress to Protect Taxpayer Interests in Federally-Funded Drug Research." Press Release. Office of the Honorable Ron Wyden, U.S. Senate. August 20, 2001. <http://www.senate.gov/~wyden/8202001%20NIH.htm>.

⁹⁰ One important characteristic of tax subsidies is that they are useful only to taxpaying firms. Hence, they are not useful to start-up firms that do not yet have an income-producing product or service.

⁹¹ National Science Board, 2000, *op. cit.*, Appendix Table 2-45.

permanent, arguing that the predictability of the credit will lead to higher R&D investments.⁹² H.R. 41 and S. 41, introduced in 2001 by a bipartisan group of Representatives and Senators, would do this. One significant impediment to making the credit permanent is the impact of a long-term obligation on the amount of discretionary federal funds available to Congressional appropriators for other uses.

S. 1049, introduced in 2001 by Senator Robert Torricelli (D-NJ), and its companion, H.R. 2153, introduced by Representative Philip Crane (R-IL) et al., would create a refundable version of a research tax credit designed to benefit smaller research-intensive companies that may not have the taxable income to benefit from current R&E credit. These bills have been referred to the Senate Committee on Finance and the House Committee on Ways and Means, respectively.

The Orphan Drug Tax Credit

The Orphan Drug Act of 1983 (described earlier under “Orphan Drugs”) includes a tax credit equal to 50 percent of qualified expenses for human clinical trials of drugs given orphan status by the FDA. The value of this credit is somewhat limited since a firm must have taxable income in the year it incurs the R&D expenses in order to qualify – many start-up firms would not have products and, hence, no taxable income. In addition, not all R&D qualifies for the credit.⁹³ As indicated earlier, the seven-year market exclusivity is the most valuable of the Orphan Drug Act’s incentives. Even with these limitations, however, the Treasury granted \$80.1 million in orphan drug tax credits in FY 1998 and \$61.4 million in FY 1997.⁹⁴

Possessions Tax Credits

Beginning in 1948, the U.S. tax code granted credits to businesses that invested in Puerto Rico and other U.S. possessions. The pharmaceutical industry extensively used one of these credits, Section 936 (referring to its location in the federal tax code). By locating facilities in Puerto Rico and attributing “non-tangible” assets such as patents to those facilities, all income derived from those assets would be free of tax in the United States. The firms would owe taxes only to the taxing authority of the U.S. possession. Because Puerto Rico’s tax rates are lower than federal U.S. rates, many drug companies made use of Section 936 tax rates. In 1993,

⁹² PhRMA, *op. cit.*, 2002, p. 17. R&D Credit Coalition, National Association of Manufacturers, *The R&D Credit Workbook*. Washington, DC. March 30, 2001.
<http://www.nam.org/tertiary.asp?TrackID=&CategoryID=693&DocumentID=22813>.

⁹³ “Qualified” R&D means that the R&D meets criteria laid out for the R&E tax credit, which excludes certain types of expenses such as software development and any management costs other than the direct supervision of R&D. In addition, this credit is only for human trials, not the laboratory research that precedes them. OTA, *op. cit.*, 1993, p. 190.

⁹⁴ This implies that during the two-year period, the firms claiming the credit engaged in \$283 million worth of clinical testing before taxes (\$141 million after taxes). In those two years, the FDA approved 36 orphan products for 39 different indications. Love, J., Palmed, M., “Costs of Human Trials: Surprising Evidence From the U.S. Orphan Drug Act.” Consumer Project on Technology. November 28, 2001.
<http://www.cptech.org/ip/health/orphan/irsdata9798.html>

Congress reduced the credit by lowering the proportion of income shielded from U.S. federal taxes from 100 percent to 40 percent. In 1995, it repealed the credit altogether for firms that make new investments in Puerto Rico, and established a 10-year phase-out for firms already benefiting from Section 936.⁹⁵

In the face of significant plant closures by U.S. firms in Puerto Rico, the island's government has proposed that American firms with a particular type of subsidiary in Puerto Rico (known as "certified foreign corporations" or CFCs) be allowed to exempt 90 percent of the income derived from Puerto Rican operations from federal taxes (H.R. 2550, introduced July 18, 2001).⁹⁶

Reimportation and Drug Prices

The particular difficulties of older Americans in paying for prescription drugs have given rise to state-level pharmaceutical assistance programs as well as proposals to create an outpatient prescription drug benefit in Medicare. Both of these topics are beyond the scope of this report. A third response has been legislation to allow the "reimportation" by wholesalers of drugs produced in the United States from other countries where prices are lower than in the United States.⁹⁷ Congress passed, and President Clinton signed on October 28, 2000, the Medicine Equity and Drug Safety Act as part of the FY 2001 agricultural appropriations (P.L. 106-387); this legislation allowed drug reimportation and appropriated \$23 million for the FDA for monitoring. However, in December 2000, U.S. Health and Human Services Secretary Shalala blocked implementation because she said she could not certify, as required in the law, that reimported drugs would be safe and that the legislation would result in significantly lower prices. In particular, she pointed to three issues:

- U.S. drug companies did not have to supply wholesalers with necessary FDA-labels for reimported products.
- U.S. drug companies could charge higher prices for U.S. drug sales to wholesalers who also reimport.
- Wholesalers would not have sufficient financial incentives to establish the infrastructure to reimport because the law would only be effect for five years.⁹⁸

⁹⁵ A companion credit, Section 30A, which provides tax credits for wages paid in Puerto Rico and other U.S. possessions, is also slated for phase-out at the end of 2005. While capital-intensive firms such as pharmaceutical companies took advantage of Section 936 credits, labor intensive industries such as clothing manufacturers tended to use Section 30A. Hoffman, K.C., "Puerto Rico Moves To Keep Attractive Tax Environment." *SupplyChainBrain.com*. September 2001. <http://www.supplychainebusiness.com/archives/9.01.regionalfocus.htm?adcode=55>.

⁹⁶ Currently, the tax code allows U.S. firms that establish a CFC in another country to exempt income from that CFC from U.S. federal taxes only if the firm reinvests the income in the CFC. Under H.R. 2550, firms would pay federal taxes on only 10 percent of income "repatriated" from a CFC. Hoffman, 2001, *op. cit.*

⁹⁷ Although much of the impetus for lawmakers' concern over high drug prices has been their impact on elderly individuals, federal legislation discussed in this section would allow everyone in the United States to purchase reimported versions of their prescribed drugs regardless of age.

⁹⁸ In July 2001, then U.S. Health and Human Services Secretary Thompson reaffirmed his predecessor's decision.

In February 2001, Representative Bernard Sanders (I-VT) et al. introduced legislation to modify and/or expand the 2000 reimportation law (H.R. 698).⁹⁹ Objections to reimportation came not only from the pharmaceutical industry, but also from the FDA, which was concerned that it could not assure the safety of drugs that left and then returned to the United States. Yet, supporters point to the fact that only a small portion of Americans are currently able to travel to purchase drugs in other countries for prices cheaper than those found in the United States. They argue that reimportation would make lower prices available to larger numbers of Americans.

⁹⁹ The House version of the FY 2002 agricultural appropriations bill included an amendment sponsored by Representative Gil Gutknech (R-MN) that would allow individuals to purchase drugs from the other most industrialized countries in person, through mail-order, by fax machine, or through the internet. The Senate bill did not contain this provision, and it was not included in the final law.

Conclusion

The American taxpayer contributes significantly to the development of new drug therapies in the United States. Although drug companies provide much of the intellectual and financial capital to bring new pharmaceuticals to market, the federal government provides:

- Patents and other types of market exclusivities. Evidence suggests that the length of time innovator firms enjoy these monopolies has grown in recent years.
- Federal funding of the nation's biomedical enterprise. Although only a small number of currently available drugs were discovered at NIH or other federal laboratories, a much larger number have depended on work funded by NIH on its own campus or in universities. Furthermore, a large portion of scientists working on new drugs were trained with federal support. A major difficulty in understanding the relative public and private roles in drug discovery is the lack of record-keeping about commercial products resulting from NIH research. As NIH's budget has doubled in recent years, one would expect that the agency's contribution to new therapies also would grow.
- Tax subsidies. Although probably less of a subsidy than are the values of market exclusivity and biomedical research funding, the R&E, orphan drug, and U.S. possessions tax credits are potentially important to the finances of individual pharmaceutical firms and the availability of new drugs.

The federal government makes these investments in order to assure patients have access to new medical therapies.¹⁰⁰ However, the cost of those therapies is an important determinant of whether patients and insurers have access to them. Newer and medically more valuable drugs have also been more expensive than earlier pharmaceuticals. As the drug R&D process continues to add to the medical arsenal, drug spending is likely to receive ever more scrutiny from policy-makers. The recent debate over reimportation is one result of that scrutiny. Finding a balance between assuring continued pharmaceutical innovation and providing access to pharmaceuticals at reasonable, affordable prices is likely to be a significant part of future policy debates.

¹⁰⁰ In addition, a strong pharmaceutical industry is an important source of jobs, productivity, and overall national economic health.

Appendix A: The Costs of Pharmaceutical R&D

In response to questions concerning the rising costs of prescription drugs, the pharmaceutical industry commonly points to the growing expense of conducting the research and development (R&D) to produce new drugs. Industry investment in R&D has indeed increased steadily over the last generation, as shown in Exhibit 3. Estimates completed in 2001 by the Center for the Study of Drug Development at Tufts University and based on data supplied by the drug industry indicate that, on average, it costs \$802 million (in 2000 dollars) to bring a new drug to market.¹⁰¹ The Tufts researchers also estimated in 1991 that the cost of bringing a new drug to market at that time averaged \$470 million (1991 dollars).¹⁰² These estimates include the cost of potential drugs that prove ineffective or unsafe and never make it to market as well as “time value” (i.e., the interest cost) of money invested over the entire R&D process. A 1993 study by the now defunct Congressional Office of Technology Assessment concluded that the *methods* used by the Tufts researchers in the 1991 study¹⁰³ are the correct way to calculate such an average cost, assuming the underlying data provided by industry are correct.¹⁰⁴

These estimates have been criticized by many groups including a detailed 2001 report by the consumer-oriented advocacy group Public Citizen in 2001.¹⁰⁵ Critics point to several areas of concern:

- Industry considers data reported to Tufts about its investments in specific drug projects to be proprietary. Hence, other researchers cannot verify it. One industry critic has recently questioned industry’s claims about the cost of conducting clinical trials. In particular, he found industry’s estimates to be higher than those based on publicly-available data from the NIH.¹⁰⁶ This raises the question of whether public policy decisions concerning

¹⁰¹ Tufts Center for the Study of Drug Development, “Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at \$802 Million.” Press Release. November 30, 2001. <http://www.tufts.edu/med/csdd/images/NewsRelease113001pm.pdf>.

¹⁰² Di Masi, J., “The Cost of Innovation in the Pharmaceutical Industry,” *Journal of Health Economics*. 10 (1991) 107-142.

¹⁰³ The Tufts researchers used the same methodologies in the 1991 and 2001 studies.

¹⁰⁴ U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks, and Rewards*. OTA-H-522 (Washington, DC: U.S. Government Printing Office. February 1993), Chapter 3. http://www.wvs.princeton.edu/~ota/ns20/alpha_f.html.

¹⁰⁵ Public Citizen’s Congress Watch, *Rx R&D Myths: The Case Against the Drug Industry’s R&D “Scare Card.”* (Washington, DC: Public Citizen. July 2001). Other criticisms of these estimates come from the Consumer Project on Technology at <http://www.cptech.org/ip/health/econ/rndcosts.html>, and Families USA, *Off The Charts: Pay, Profits and Spending by Drug Companies*. Publication No. 01-104. (Washington, DC: Families USA. 2001) at <http://www.familiesusa.org/media/pdf/drugceos.pdf>, accessed June 19, 2002.

¹⁰⁶ Love, J., “Call for More Reliable Costs Data on Clinical Trials.” (Washington, DC: Consumer Project on Technology. 1997). <http://www.cptech.org/pharm/marketletter.html>.

pharmaceuticals should be based on information for which industry is not publicly accountable.

- The OTA study found potential variations among firms in how they account for R&D costs. Some practices, such as decisions to account for capital expenditures relatively late in the R&D process, may lead to underestimates in R&D costs. However, differences can also exist in how and when manufacturers begin to attribute R&D costs to particular drugs projects as opposed to attributing costs to general basic research expenditures. Because of the “time value” of money and the long time it can take for a potential pharmaceutical to reach the market, early expenditures can constitute a substantial portion of the total cost of bringing a drug to market. Although these variations in how manufacturers attribute their R&D costs conform to accounting and Internal Revenue Service (IRS) standards, small differences can greatly affect the ultimate cost estimates of bringing a drug to market. As OTA pointed out, firms with an understanding of the policy uses to which these estimates are put would have a significant incentive to account for costs in a manner to maximize early expenditures.¹⁰⁷ The Public Citizen report also questions whether the Tufts study understates the likelihood that a given drug in R&D will actually reach the market and overstates the amount of time it takes the FDA to approve new drugs. If Public Citizen were correct, the Tufts estimates would be too high.¹⁰⁸
- The Public Citizen report also points out that none of the Tufts estimates take into account tax credits and other federal subsidies outlined in this paper.¹⁰⁹
- Some critics have questioned the value of some of the clinical research in which pharmaceutical companies engage. In particular, they claim that many clinical studies are done after a drug has been approved for marketing. Industry claims that such research is increasingly required by the FDA as a condition for a drug’s approval and that the studies are important in identifying serious side effects that are uncommon enough to be missed in studies done prior to a drug’s approval. The critics acknowledge that some post-marketing research is intended to assure patient safety, but they claim many such studies and similar types of expenditures are primarily intended to promote the product among physicians and should be considered marketing expenses rather than R&D.¹¹⁰

¹⁰⁷ U.S. Congress, Office of Technology Assessment, *op. cit.*, 1993, p. 58.

¹⁰⁸ Public Citizen’s Congress Watch, *op. cit.*, 2001, pp. i-ii.

¹⁰⁹ Public Citizen’s Congress Watch, *op. cit.*, 2001, pp. i-ii.

¹¹⁰ Public Citizen’s Congress Watch, *op. cit.*, 2001, p. 11. Angell, M, “The Pharmaceutical Industry—To Whom Is it Accountable?” *The New England Journal of Medicine*. 342 (June 22, 2000), pp. 1902-1904. U.S. Senate Special Committee on Aging, U.S. Senate, “The Drug Manufacturing Industry: A Prescription For Profits,” September 1991 at <http://www.rxpolicy.com/studies/pryor.pdf>, accessed June 19, 2002, pp. 9-10.

- Other analysts point to the growing trend among pharmaceutical companies to make minor changes in a drug prior to its patent expiration in order to extend its market share.¹¹¹ This trend is discussed in greater detail in the section of this report on generic competition and patent extensions. Although such R&D expenditures do not represent true innovation, they nevertheless inflate the estimates of bringing a new drug to market.

¹¹¹ National Institute for Health Care Management Research and Educational Foundation, *Changing Patterns of Pharmaceutical Innovation*. (Washington, DC: National Institute for Health Care Management. 2002). <http://www.nihcm.org/innovations.pdf>.

Appendix B: Selected Federal Laws Relevant to the Development of New Pharmaceuticals

<u>Year</u>	<u>Law</u>
1962	Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (P.L. 87-781). Established the current standards for marketing pharmaceuticals in the United States, including requiring manufacturers to demonstrate scientifically the efficacy of drug products. Previously, manufacturers were only required to demonstrate safety.
1980	Stevenson-Wydler Technology Innovation Act of 1980 (P.L. 96-480). Required all federal laboratories to spend at least 0.5% of their research budgets on efforts to transfer technology they develop to the private sector for potential commercialization.
1980	Patient and Trademark Amendments of 1980, also known as the Bayh-Dole Act (P.L. 96-517). To promote the practical application and commercialization of intellectual property produced with federal funding this legislation allowed the patenting of such intellectual property.
1981	Economic Recovery Act of 1981 (P.L. 97-34). Included the research and experimentation tax credit for firms that increased their expenditures for qualifying research and development in a given tax year. Renewed and restricted somewhat in subsequent years, the current version of the tax credit expires in 2004.
1983	Orphan Drug Act (P.L. 97-414). Created incentives for the development of therapies for rare diseases, defined as conditions affecting fewer than 200,000 individuals in the United States. Incentives include: (1) seven years of exclusive marketing for the first manufacturer receiving FDA approval for a treatment for an orphan condition; (2) a 50-percent tax credit for testing orphan drugs in humans; (3) an FDA-run research grants program; and (4) technical assistance from the FDA in the design of human trials and preparation of marketing applications to the FDA.
1984	Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act (P.L. 98-417). To promote competition for brand name drugs by generic equivalents, established an Abbreviated New Drug Application (ANDA) process. The law also: (1) allowed brand name manufacturers to receive patent extensions of up to five years to compensate for unusually long FDA marketing

approval times (with the total period between market approval and patent expiration not to exceed 14 years); (2) a ban on generic manufacturers from using brand manufacturers' data in their ANDAs for five years for new compounds and three years for existing compounds; and (3) a maximum two-year (rather than five-year) patent term extension for promising drug compounds already in clinical trials or under FDA pre-marketing review.

- 1986 Federal Technology Transfer Act of 1986 (FTTA), (P.L. 99-502).** In order to promote transfer of technology developed in federal laboratories, gave federal scientists rights to some royalties from their patented discoveries and permitted formal cooperative research and development agreements (CRADAs) between federal laboratories and private organizations (e.g., for-profit firms). Private CRADA partners are also given the right to exclusive licenses to patented technologies produced as part of the CRADA.

- 1992 Prescription Drug User Fee Act of 1992 (PDUFA), (P.L. 102-571).** Imposed user fees on brand name manufacturers submitting pre-marketing applications to the FDA with funds raised used to extend FDA resources and expedite approvals.

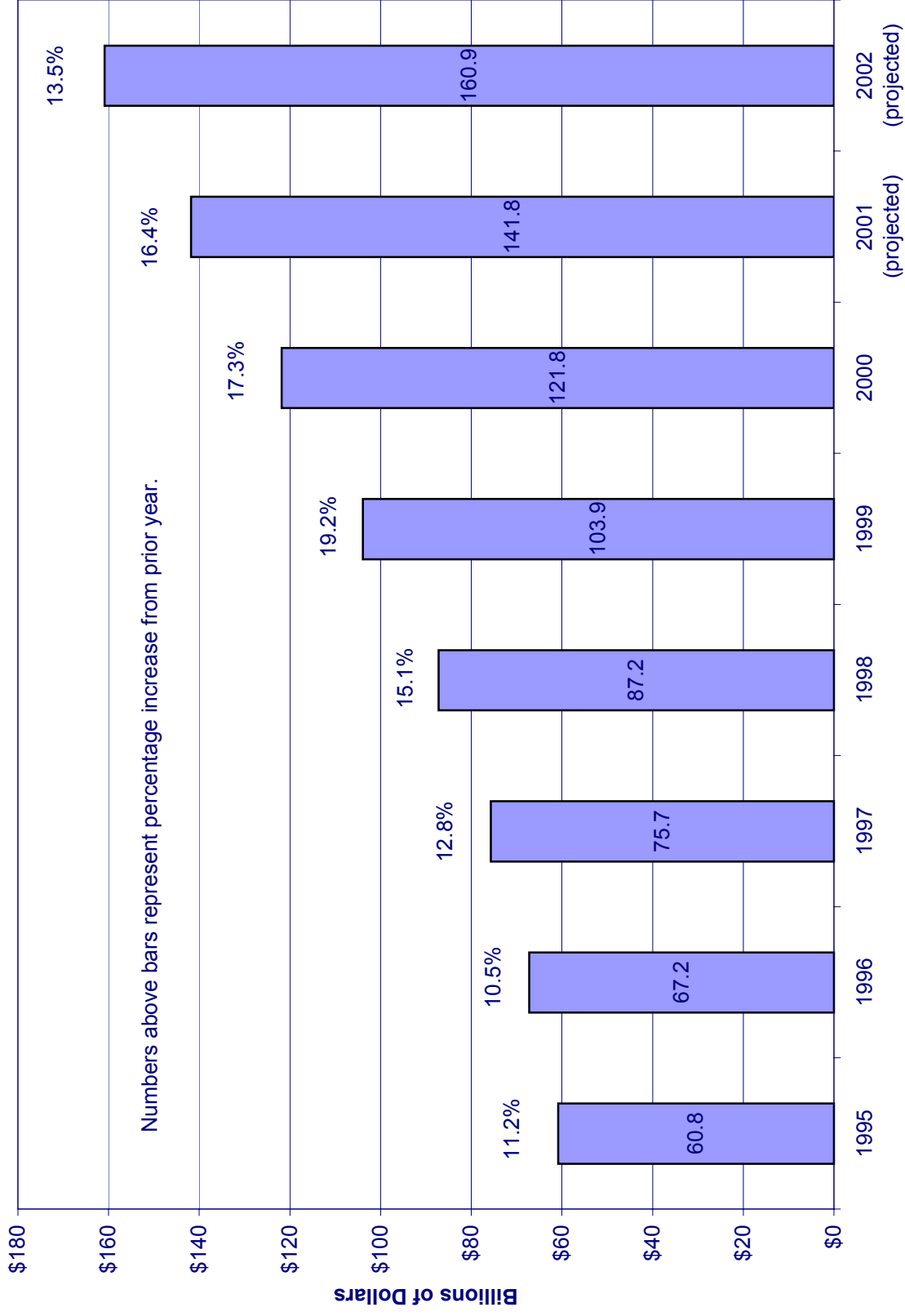
- 1994 Uruguay Round Agreements Act (P.L. 103-465).** Changed the period of U.S. patents from 17 years beginning when the patent is issued to 20 years beginning when the patent application is filed.

- 1997 Food and Drug Administration Modernization Act of 1997 (FDAMA), (P.L. 105-115).** In addition to reauthorizing and expanding the user fee program for an additional five years to allow FDA to hire more reviewers, the law: (1) established a new "mission statement" for the FDA to promote and protect public health; (2) made additional changes in FDA procedures to expedite the review of new drug and biologicals; (3) set performance standards for answering industry inquiries and reviewing marketing applications; (4) established a paperless system for filing paperwork with the agency; and (5) allowed for six additional months of marketing exclusivity after patent expiration for manufacturers who conduct studies about the safety and efficacy of such drugs in children (known as the pediatric exclusivity clause).

- 2000 American Inventors Protection Act of 1999 (enacted as part of the FY 2000 Consolidated Appropriations Act, P.L. 106-113).** Added one day to a patent for each day over 3 years it takes the U.S. Patent and Trademark Office to issue the patent.

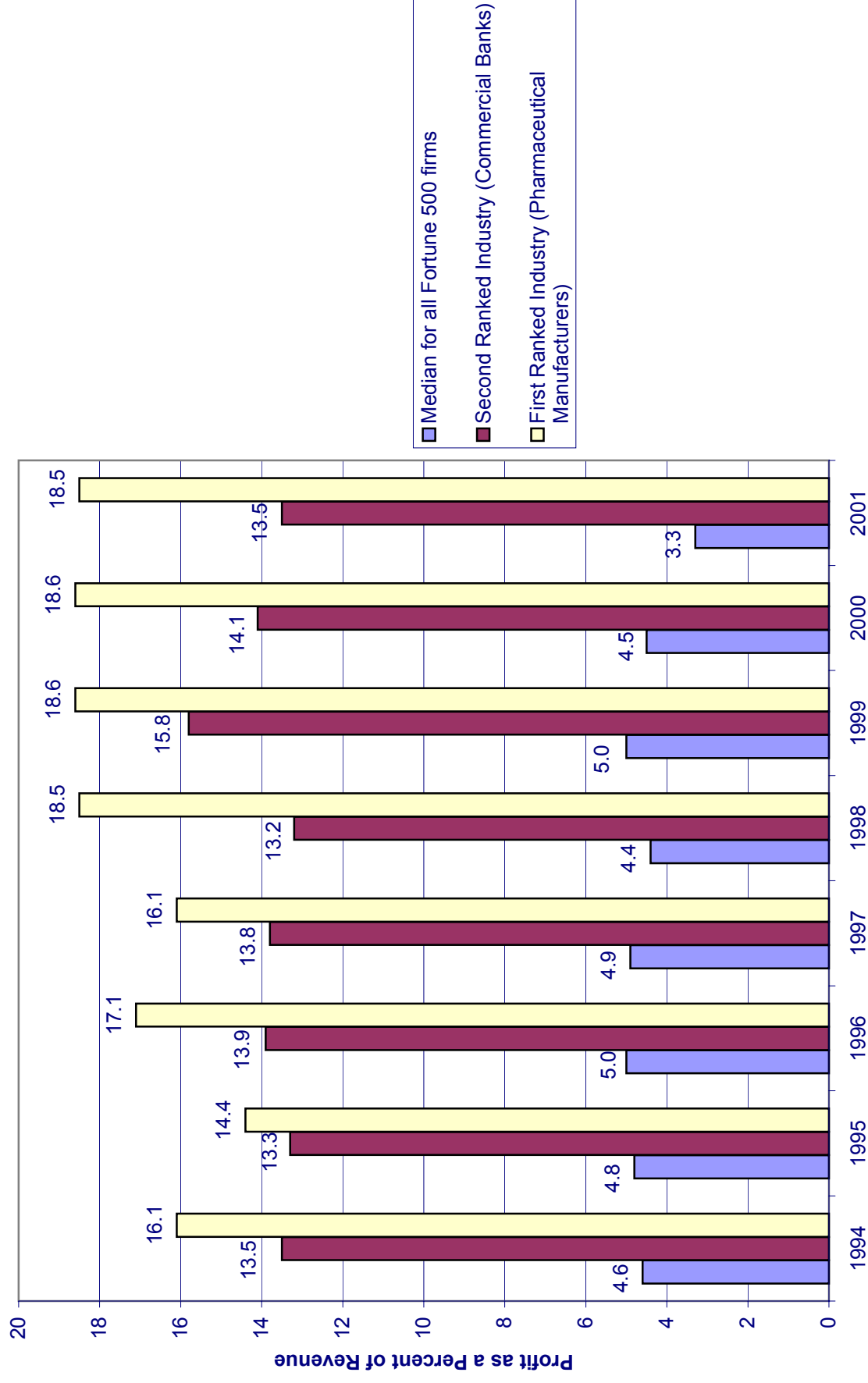
- 2000 Medicine Equity and Drug Safety Act of 2000 (enacted as part of the FY 2001 Agricultural Appropriations legislation, P.L. 106-387).** Authorized, upon a guarantee of safety by the Secretary of Health and Human Services, the “reimportation” by wholesalers of drugs manufactured in the United States from countries where drug prices are lower than in the United States. Not implemented because the Secretary indicated that safety could not be guaranteed.
- 2002 Best Pharmaceuticals for Children Act (P.L. 107-109).** Extended through 2007 the pediatric exclusivity clause first enacted in 1997.
- 2002 Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188).** Among other provisions, reauthorized FDA user fees through 2007.

Exhibit 1: National Expenditures and Percent Increase from Prior Year for Prescription Drugs, 1995-2002



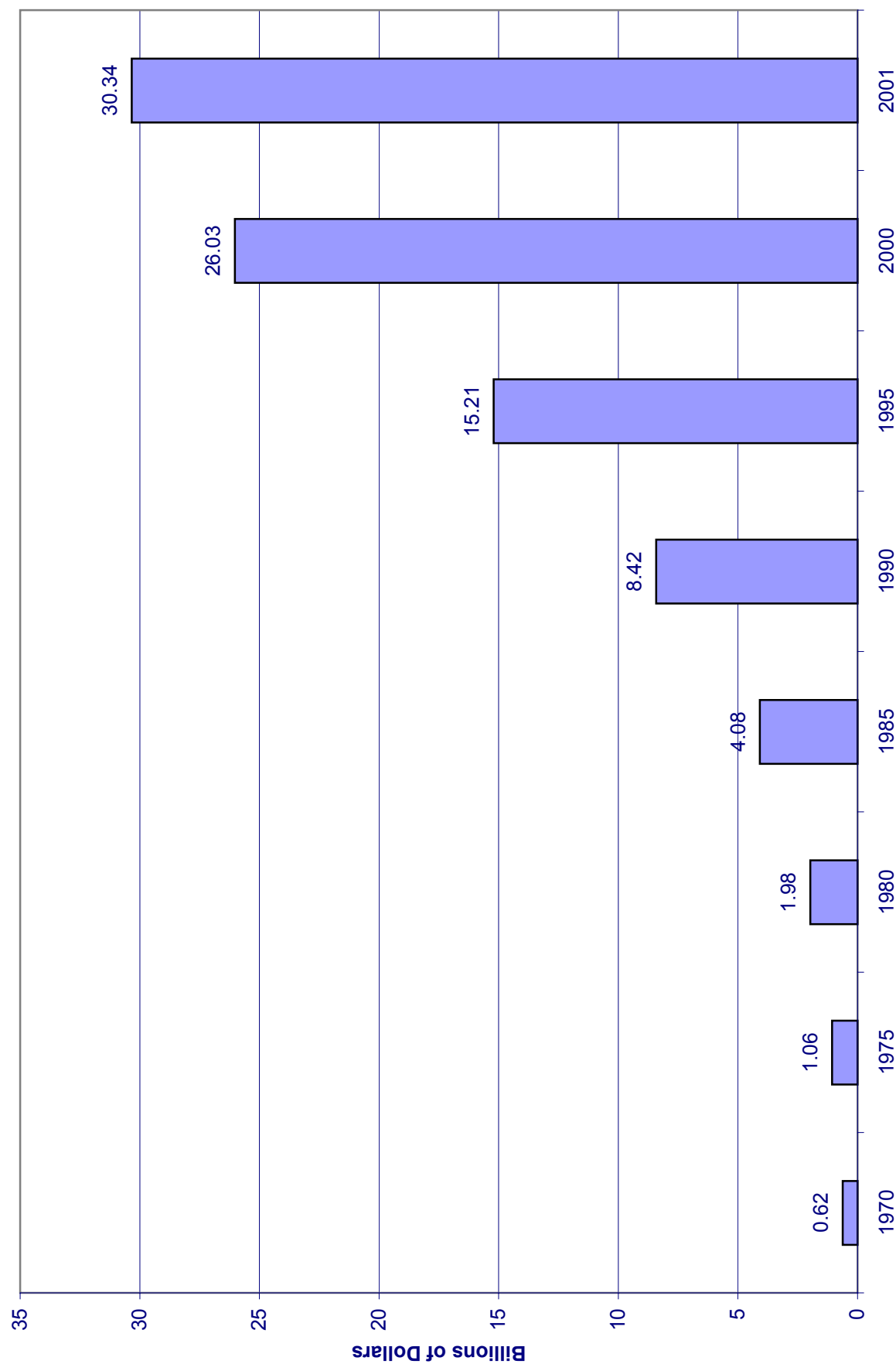
Source: National Health Expenditures, Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group, 2002, at <http://www.hcfa.gov/stats/NHE-Proj/proj2001/tables/t11.htm>.

Exhibit 2: Profitability Among Pharmaceutical Manufacturers Compared to Other Industries, 1994-2001



Source: Williams, C, Treloar, J, *Trends and Indicators in the Changing Health Care Marketplace*, 2002. (Menlo Park, CA: The Henry J. Kaiser Family Foundation, May 2002), p.46.

Exhibit 3: R&D, U.S. Research-Based Pharmaceutical Companies, 1970-2001



Source: Pharmaceutical Research and Manufacturers of America, *Pharmaceutical Industry Profile*, 2002, p. 75.

Exhibit 4: Mean FDA Approval Times for New Drug Applications, 1988-2001

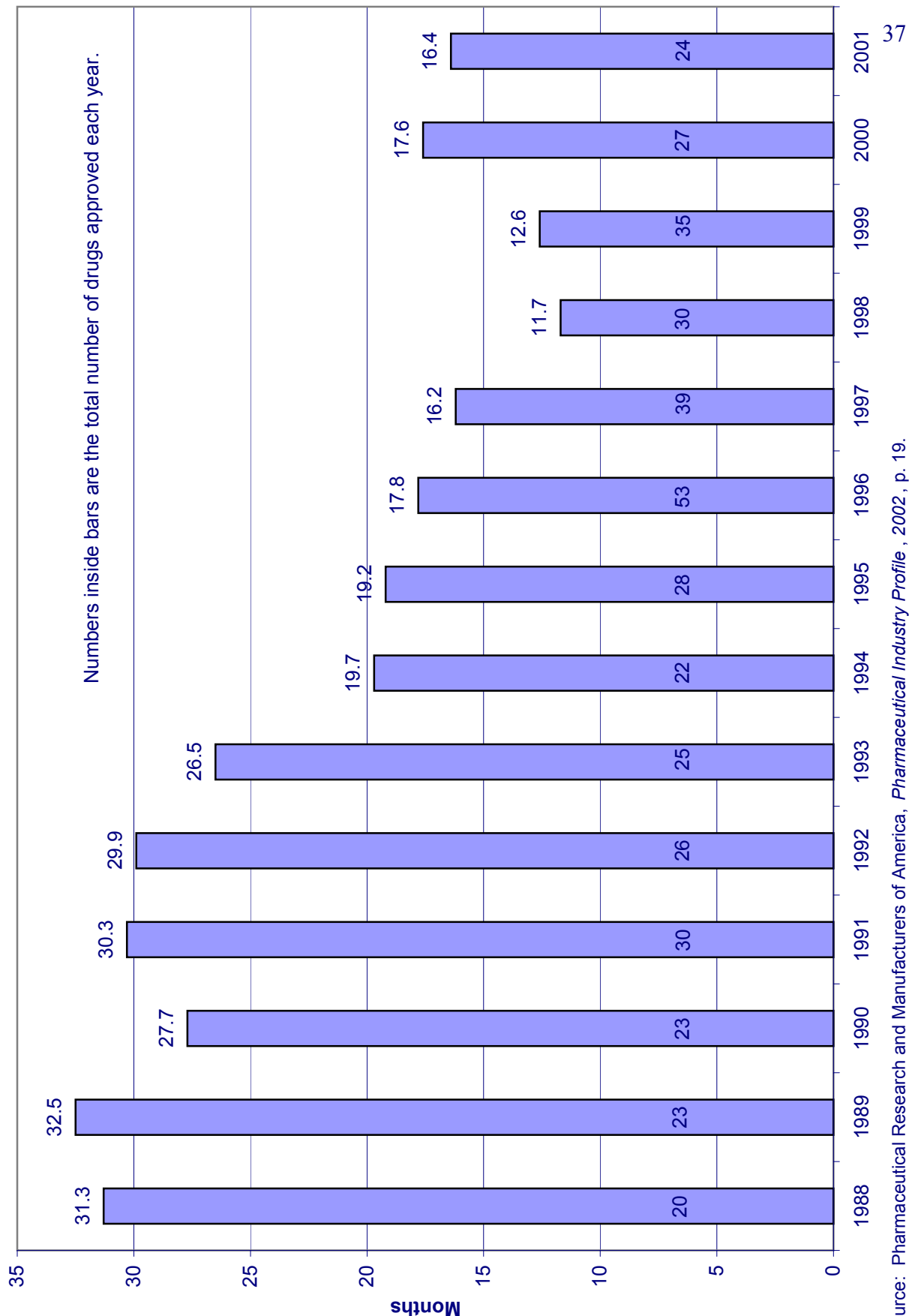
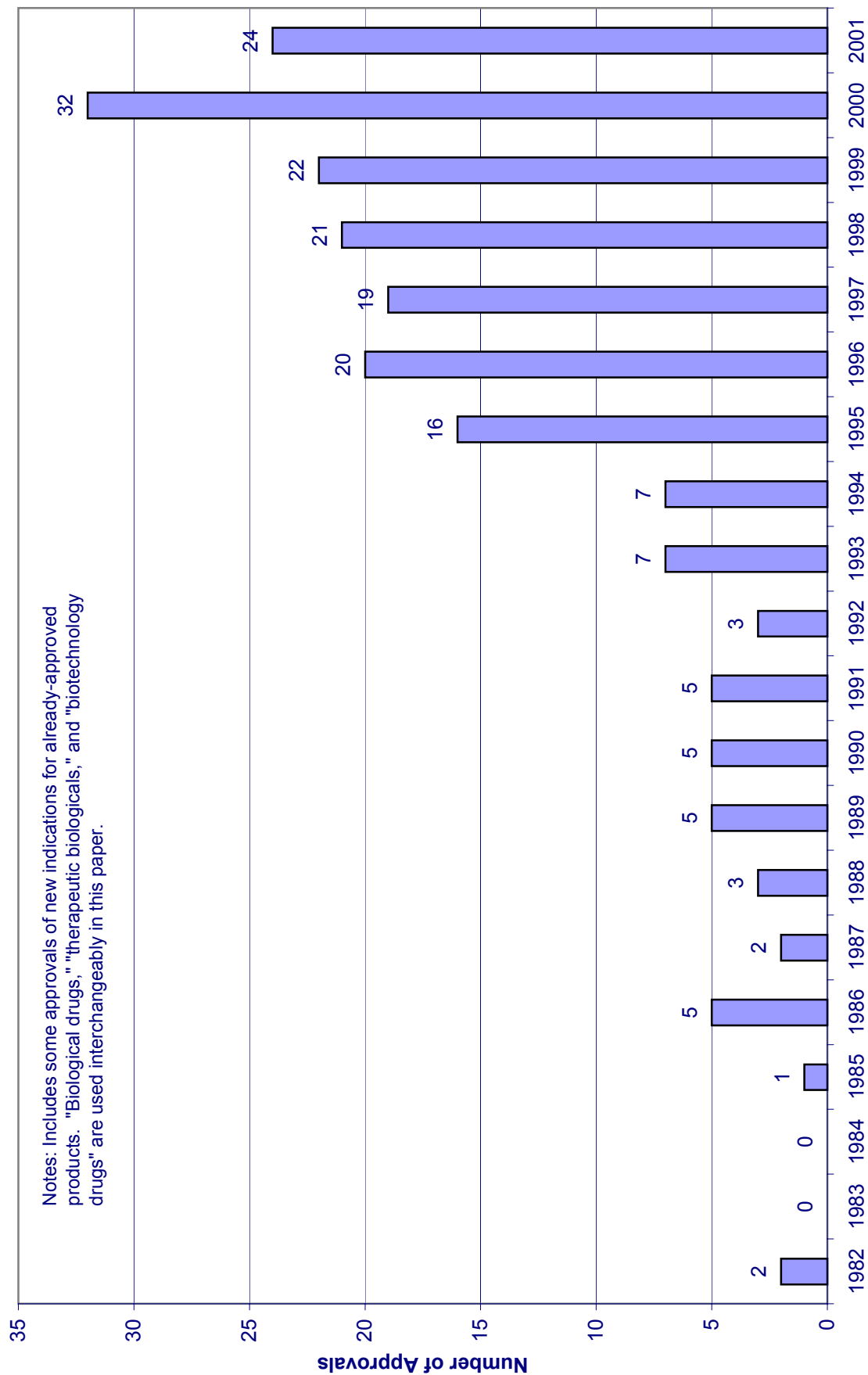
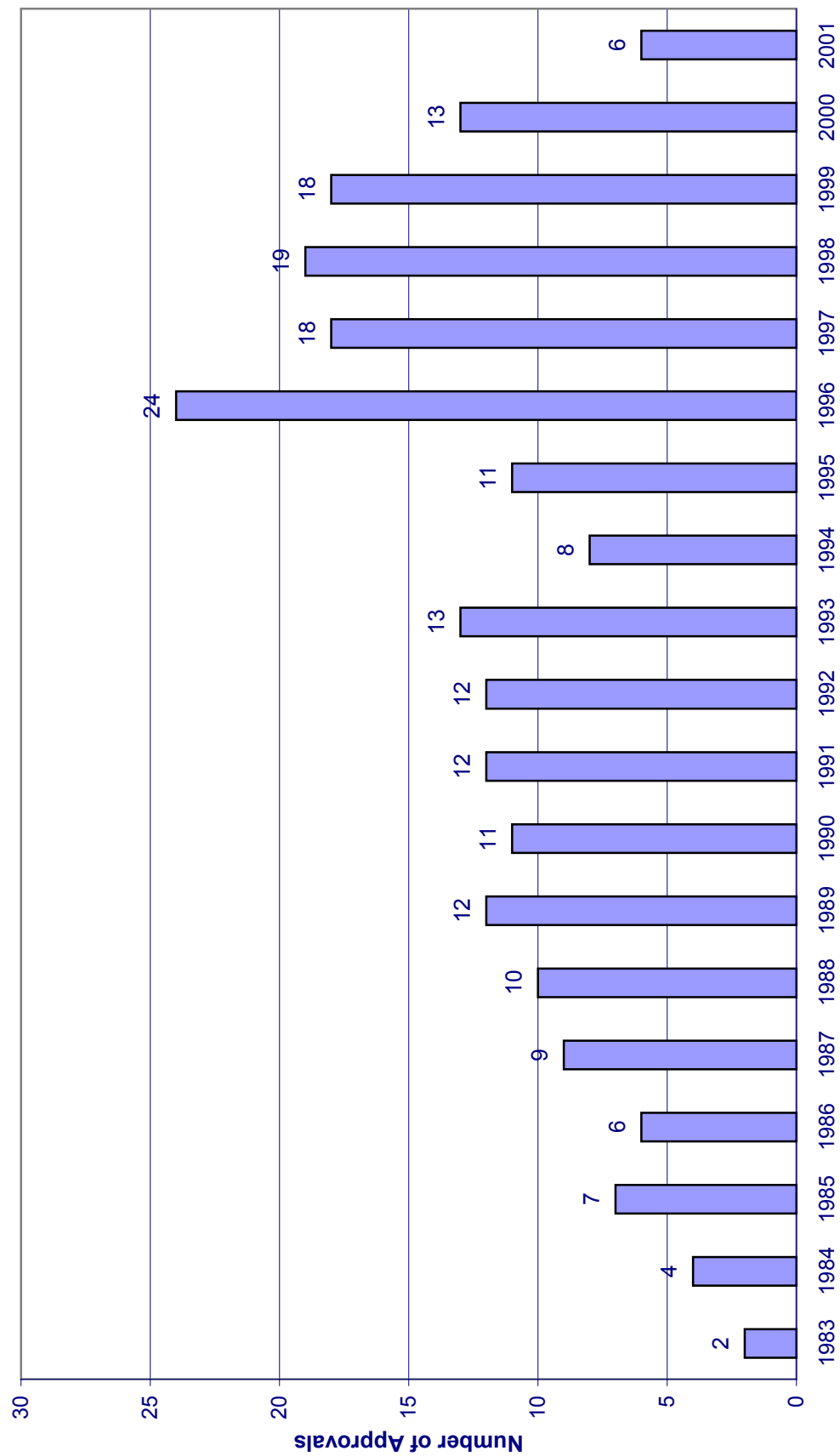


Exhibit 5: New FDA Approvals for Biological Drugs and Vaccines, 1982-2001



Source: Biotechnology Industry Organization (BIO), 2002, at <http://www.bio.org/er/statistics.asp>.

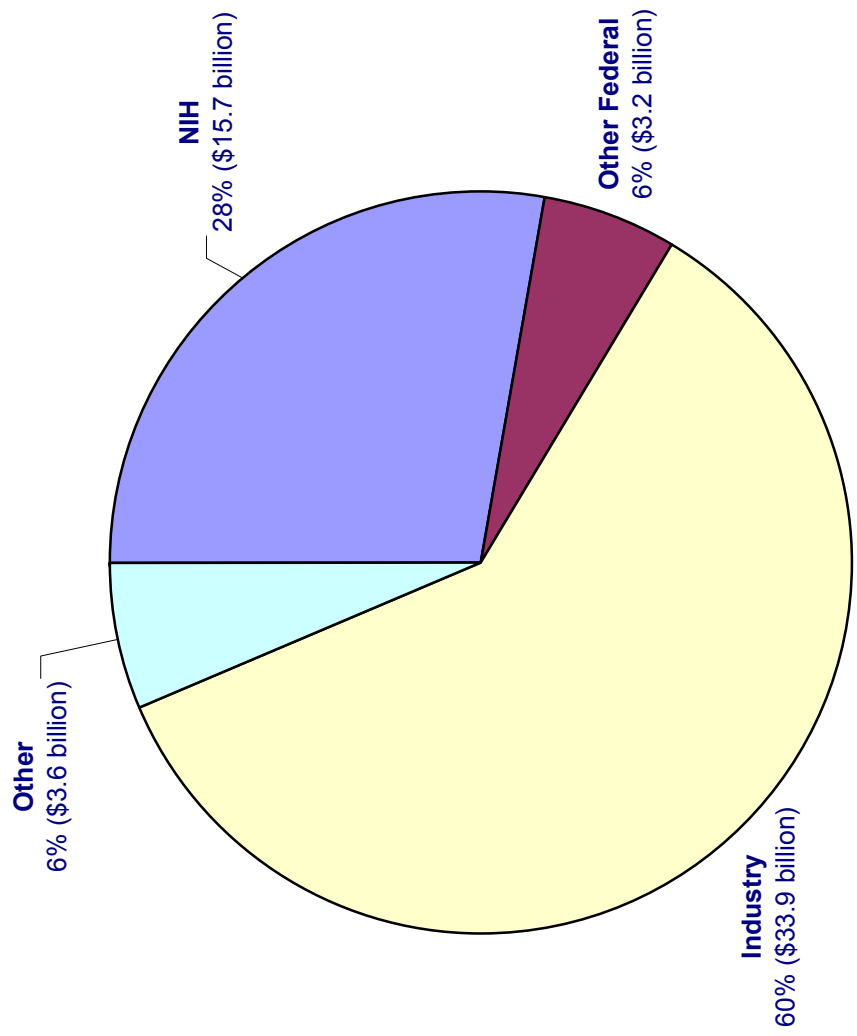
Exhibit 6: FDA Approvals of Orphan Products, 1983-2001



Notes: Excludes 9 products for which approval date is not given in FDA database. At least some of these products were withdrawn from the market.

Source: U.S. Food and Drug Administration at <http://www.fda.gov/orphan/designat/Approvals.htm>, 2002

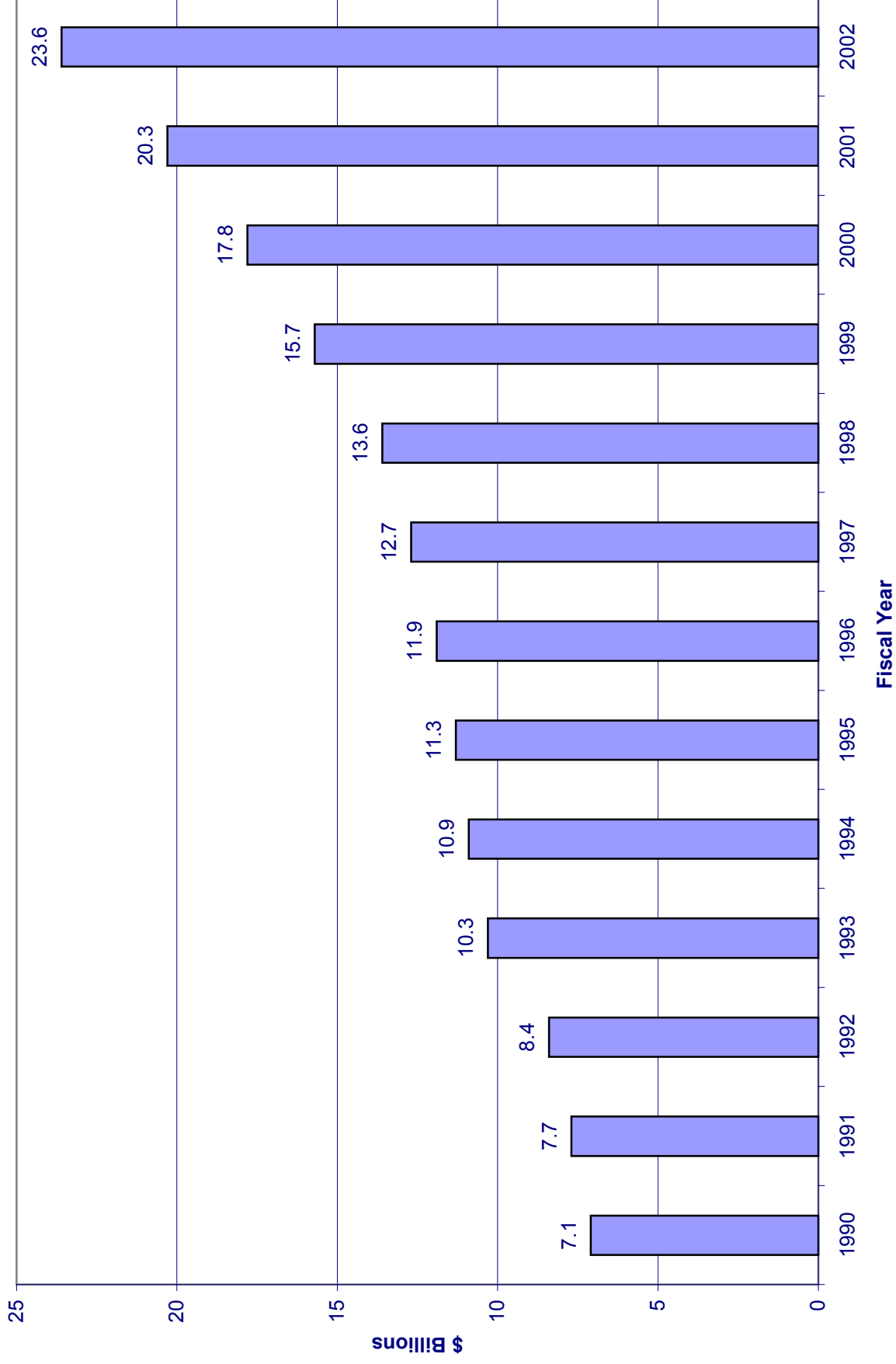
Exhibit 7: Medical and Health R&D Expenditures in the United States, FY1999



Total Medical and Health R&D, FY 1999 = \$56.4 billion

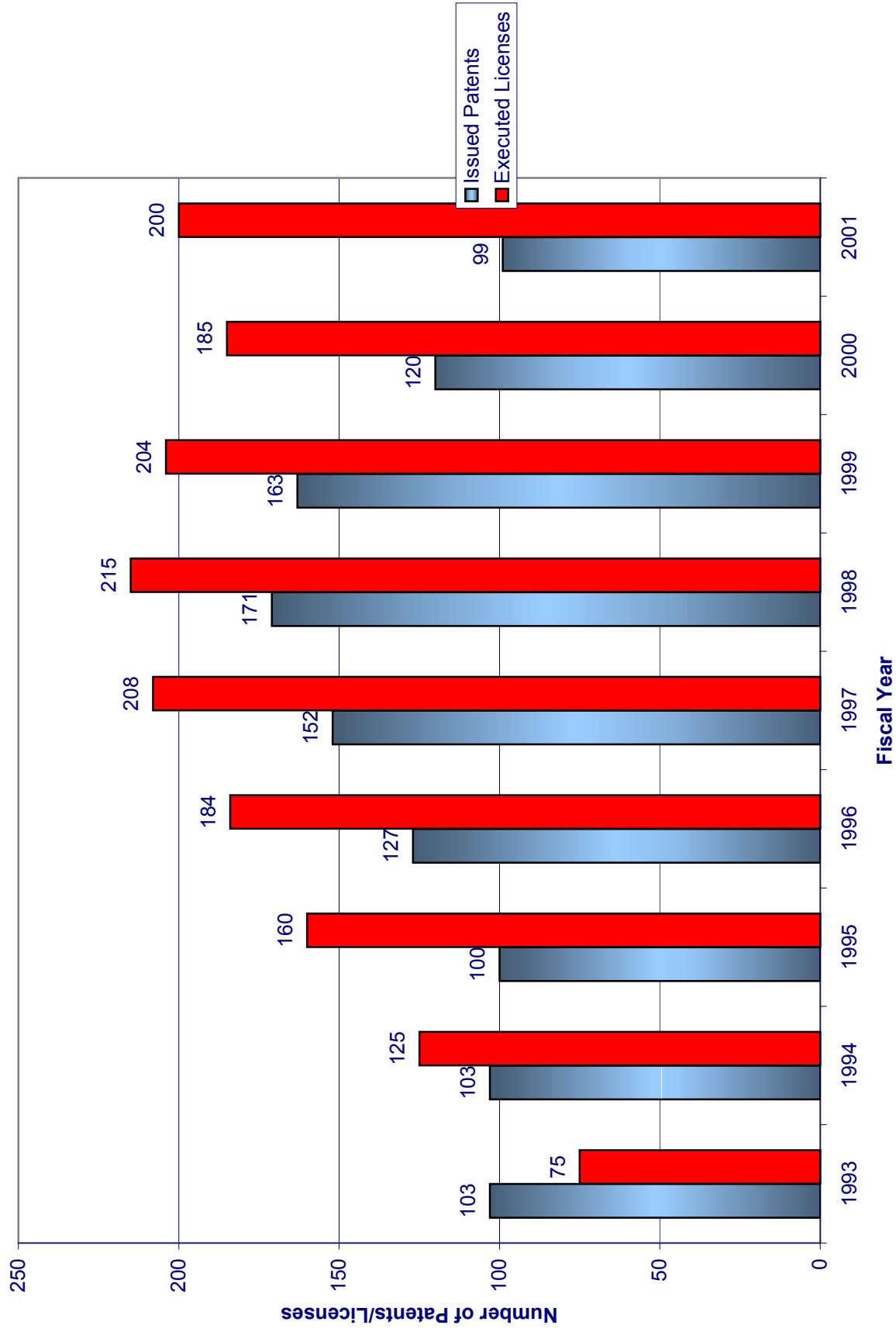
Notes: "Other" includes universities' own funds, private foundations, voluntary health associations, and private research institutes' own funds.
Source: Research! America, "How Much is Really Spent on Medical and Health Research?" at <http://www.researchamerica.org/media/briefs/spent.html>.

Exhibit 8: NIH Appropriations, FY 1990-FY 2002



Sources: NIH Data Book 1993, NIH Publication 93-1261, September 1993; NIH Office of the Budget, 2002. Ghent, B. *National Journal News Service*, "Bid to Expand Mental Health Benefits Fails in Labor-HHS Conference," December 18, 2001, at <http://nationaljournal.com/members/markups/2001/12/200135204.htm>.

Exhibit 9: NIH Technology Transfer Activities, FY 1993-FY 2001

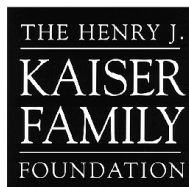


Source: NIH Office of Technology Transfer, 2002, at <http://ott.od.nih.gov/NewPages/TTstats01.pdf>.

Exhibit 10: Royalties from Licenses on NIH Patents, FY 1993-FY 2001



Source: NIH Office of Technology Transfer, 2002, at <http://ott.od.nih.gov/NewPages/TTstats01.pdf>.



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