Global Drug Discovery: Europe Is Ahead

A reanalysis of data from 1982–2003 contradicts the claim that U.S. drug firms overtook European firms in pharmaceutical innovation.

by Donald W. Light

ABSTRACT: It is widely believed that the United States has eclipsed Europe in pharmaceutical research productivity. Some leading analysts claim that although fewer drugs have been discovered worldwide over the past decade, most are therapeutically important. Yet a comprehensive data set of all new chemical entities approved between 1982 and 2003 shows that the United States never overtook Europe in research productivity, and that Europe in fact is pulling ahead of U.S. productivity. Other large studies show that most new drugs add few if any clinical benefits over previously discovered drugs. I discuss ways in which Congress, employers, and insurers can increase the value of drugs and revitalize the U.S. pharmaceutical industry. [*Health Affairs* 28, no. 5 (2009): w969–w977 (published online 25 August 2009; 10.1377/hlthaff.28 .5.w969)]

FOR MORE THAN A DECADE, industry and official reports have concluded that the United States has overtaken Europe in the discovery of new drugs, commonly defined as new chemical entities (NCEs). "Europe risks to be relegated into the fringe of the industry," concluded a seminal report that has shaped European policy.[1] "The United States has become the dominant player," the European trade association reported in 2008, as U.S. research investments grew 5.2 times from 1990 to 2007 compared to 3.3 times in Europe.[2] Reinforcing this view, Henry Grabowski and Richard Wang examined all new chemical entities discovered between 1982–1992 and 1993–2003 and concluded that U.S. firms had overtaken their European counterparts.[3] They also concluded that although the number of new chemical entities declined, their quality is high and has increased. In other words, most new drugs that are discovered are better than existing drugs, and most come from the United States.

This paper offers a new perspective based on a reanalysis of Grabowski and Wang's key findings and large studies of clinical quality over many years. It thus poses important challenges to widely held American beliefs about U.S. dominance in pharmaceutical research productivity and about the superior quality of those

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new drugs. The findings suggest that Congress and large purchasers are motivating companies to develop and market drugs that add little value, instead of rewarding true added value. This is not good for the long-term vitality of the industry or for those paying too much for too little.

Research Productivity: The Basic Picture

Let us start with the findings of Grabowski and Wang based on their comprehensive data set from IMS Health of all 919 new chemical entities approved between 1982 and 2003.[4] They used various criteria to identify which were "global" (introduced into four or more of the Group of 7, or G7, countries), first-in-class, biotech, and orphan (those developed to treat rare, or orphan, diseases) NCEs. New chemical entities were assigned to the country in which the headquarters of the company that first launched them was located. This resulted in an exhibit showing how many of each type were discovered in Europe, the United States, or Japan for 1982–1992 and 1993–2003. The present reanalysis accepts their data and definitions in order to examine the percentages and ratios of innovation.[5]

If one simply calculates the percentage of NCEs credited to the United States, Europe, and Japan, one sees in Exhibit 1 that the U.S. share of all NCEs rose dramatically from the first period to the second, while the European and Japanese shares declined. The United States gained in global, first-in-class, biotech, and orphan NCEs as well.[6] One can see, however, that European research productivity scarcely declined, and Europe continued to dominate in discovering all NCEs as well as the highly profitable global NCEs.

Clearly, the United States did not overtake Europe in discovering new chemical entities, and European researchers lost less ground than either Europeans or Americans believe.[7] Despite the appeal of launching first in the big, highly profit-

EXHIBIT 1
Percentage Of New Chemical Entities (NCEs) Discovered In The United States, Europe, And Japan, During Two Time Periods (1982–1992 And 1993–2003)

	United States		Europe		Japan	
Type of NCE	**82–92**	**93–03**	**82–92**	**93–03**	**82–92**	**93–03**
All	25.3	35.9	48.4	43.3	26.3	20.8
Global	37.3	39.5	55.9	54.6	6.6	5.8
First-in-class	46.2	50.0	44.2	45.0	9.6	4.5
Biotech	45.0	53.6	30.0	33.3	25.0	13.0
Orphan	50.0	57.4	45.0	42.6	5.0	0.0

SOURCE: Author's calculations of data from H.G. Grabowski and Y.R. Wang, "The Quantity and Quality of Worldwide New Drug Introductions, 1982–2003," *Health Affairs* 25, no. 2 (2006): 452–460, Exhibit 4, minus "rest of world."

NOTES: Because the rest of the world is not shown here, percentages by period for each type of NCE represent percentages of 100, with the universe being the United States, Europe, and Japan. For example, for 1982–92, the percentages for all NCEs (25.3 U.S., 48.4 Europe, and 26.3 Japan) add up to 100 percent.

able U.S. market, where companies face the fewest delays to market and can charge the highest prices, overall NCE research productivity in Europe using Grabowski and Wang's criteria and data was greater, even in the later period.

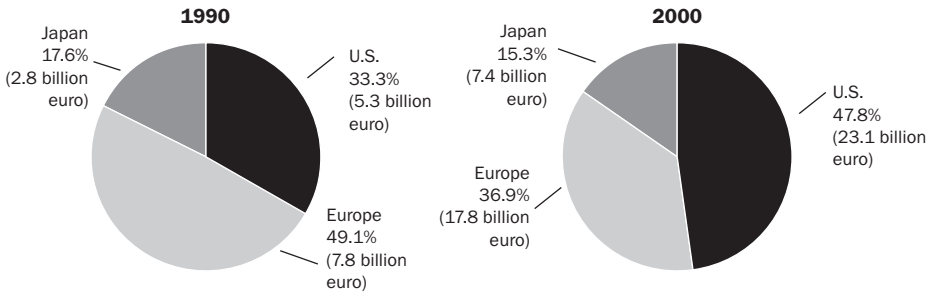
Research Productivity On A Level Playing Field

Research productivity and total funding are often confounded, as in the typical claim that "the U.S. has established itself firmly as the key innovator in pharmaceuticals since 2000."[8] To what degree is this a self-fulfilling prophecy resulting from the industry's pouring more money into American research and development (R&D), and to what degree are American labs and teams becoming more innovative, dollar for dollar?

A simple but important measure of research productivity would compare the proportion of industry R&D funding for the United States, Europe, and Japan to the proportion of new chemical entities in each. The European Federation of Pharmaceutical Industries and Associations has culled investment figures for 1990 and 2000 reported by member companies to the U.S., Japanese, and European trade associations and corrected for exchange rates.[9] Because no annual figures are given, these can approximate funding distributions for the first and second decades analyzed by Grabowski and Wang; thus, they can be used to roughly calculate the relationship between research productivity and funding.[10]

As shown in Exhibit 2, pharmaceutical companies increased their R&D investments in the United States from about a third of the three-country total in 1990 to half in 2000. R&D investment in Europe dropped twelve percentage points during the decade, and investment in Japan declined around two percentage points. Absolute numbers increased everywhere because companies reported a rapid increase in total R&D investments, from 15.9 billion euro (US$22.4 billion) in 1990 to 48.3 billion euro (US$68.0 billion) in 2000.

EXHIBIT 2
Percentage Of Total Drug Research And Development (R&D) Funds Invested In The United States, Europe, And Japan, 1990 And 2000



SOURCE: European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures*, 2008 ed. (Brussels: EFPIA, 2008). Company-reported figures were converted to euro.

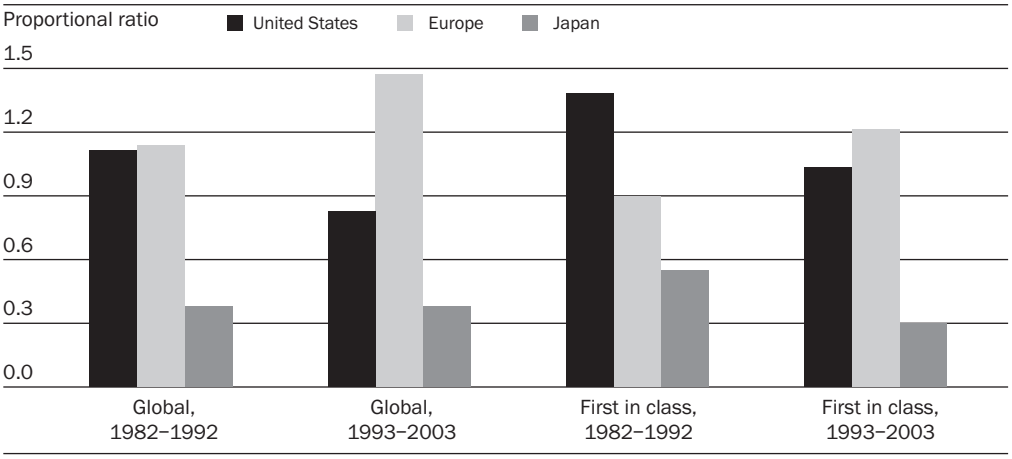
Overall research productivity can be measured by the proportion of new chemical entities to the proportion of R&D investment in the three countries. For example, if U.S. research teams received 33 percent of the budget, they should discover about 33 percent of all NCEs—a ratio of 1.0. By dividing the percentage of all NCEs in Exhibit 1 by the percentage invested, one can see that the United States discovered far fewer NCEs than its proportional share of funding: 0.76 (25.3/33.3) in the first period and 0.75 in the second. Europe's ratio of all NCEs to investment went from 0.99 in the first period to 1.17 (43.3/36.9) in the second. Japan's proportionate ratio was the highest: 1.49 in the first period and 1.36 in the second.

The big news in terms of innovation and international policy is the low and flat U.S. productivity and the high Japanese productivity. Of course, these ratios are constantly changing, and there is a lagged effect; however, Grabowski and Wang's conclusions about U.S. dominance are not supported by their own data.

How did the United States, Europe, and Japan perform for global and first-in-class new chemical entities? In global NCEs, European research productivity was about the same as U.S. productivity in the first period but increased by 30 percent in the second period (1993–2003), while U.S. research productivity declined 26 percent (Exhibit 3). In first-in-class drugs, European relative innovativeness moved from well behind the United States in the first period to well ahead in the second. These are the most commercially and therapeutically important types of new chemical entities.

In biotech products, European researchers became much more innovative in the

EXHIBIT 3
Proportional Ratio Of Global And First-In-Class New Chemical Entities (NCEs) To Research And Development Industry Funding In The United States, Europe, And Japan, In Two Time Periods (1982–1992 And 1993–2003)



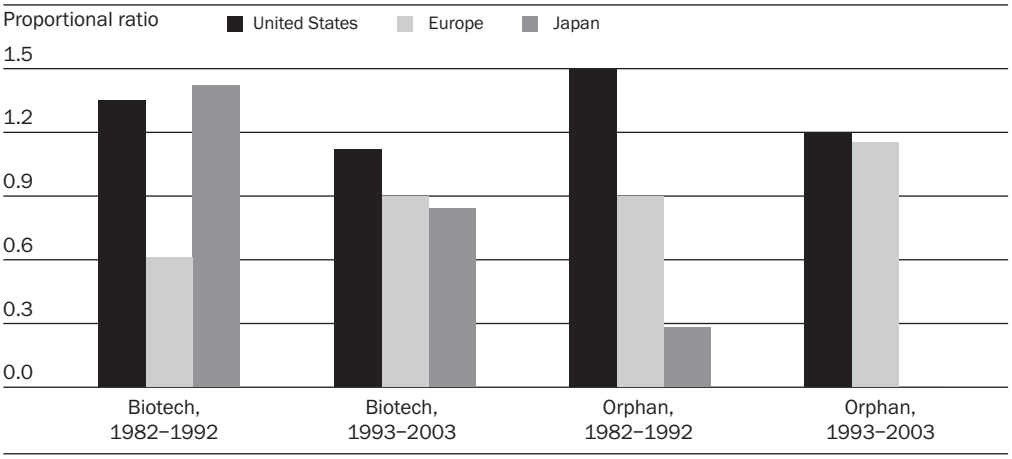
SOURCE: Author's analysis based on data in Exhibits 1 and 2.
NOTES: 1.00 equals innovation proportionate to investment, as shown in Exhibit 2. Percent change in productivity from first to second time period: Global, U.S. −26%; Europe, 30%, Japan, zero. First in class, U.S. −25%; Europe, 36%; Japan, −40%.

second period but did not catch up with their U.S. counterparts, even though U.S. productivity declined (Exhibit 4). In orphan drugs, proportional European research productivity gains and U.S. declines resulted in Europe's moving from well behind the United States to about even in the second period. Overall, these results do not support the claim that "U.S. firms overtook their European counterparts in innovative performance of first-in-class, biotech, and orphan products."[11]

Evidence of European research productivity would be stronger if one corrected for Grabowski and Wang's ruling out first-in-class new chemical entities launched in Europe or Japan but not yet available in the United States, while ruling these drugs in if launched in the United States but not in Europe or Japan. They do not disclose how many of these there were. Likewise, they excluded orphan products not yet available in the United States but included orphan drugs available in the United States but not in Europe or Japan. A third source of possible bias favoring U.S. productivity comes from assigning new chemical entities to the country in which the launching company is headquartered. This tends to favor the United States because more companies have located there than in Europe or Japan since 1982 through mergers, acquisitions, and strategic business decisions. Twelve of the twenty largest companies are headquartered in the United States.

To summarize, this reanalysis provides strong, general evidence that U.S. firms have not overtaken their European counterparts in pharmaceutical innovation. European research productivity has actually increased in proportion to funds received and would prove stronger still if new first-in-class and orphan drugs

EXHIBIT 4
Proportional Ratio Of Biotech And Orphan New Chemical Entities (NCEs) To Research And Development Industry Funding In The United States, Europe, And Japan, In Two Time Periods (1982–1992 And 1993–2003)



SOURCE: Author's analysis based on data in Exhibits 1 and 2.
NOTES: 1.00 equals innovation proportionate to investment, as shown in Exhibit 2. Percent change in productivity from first to second time period: Biotech, U.S. −17%; Europe, 48%, Japan, −41. Orphan, U.S. −20%; Europe, 25%; Japan, −100%.

launched in Europe but not the United States had been included. Given the new institutes in European countries that bring together applied scientists from industry and academe to translate discoveries into drugs, such as Top Institute (TI) Pharma in the Netherlands; Karolinska Institutet Innovations in Stockholm, Sweden; and the broader European Innovative Medicines Initiative, returns on R&D investment in Europe may increase further during the next decade of 2004–2014.[12]

No Good Evidence Of Better Quality

The claim that most new drugs are of high quality or "important" for patients is puzzling, because Grabowski and Wang never really define what they mean by "quality," and my extensive correspondence with Grabowski produced no clear answer. From the perspective of patients, physicians, and health plans, "quality" means that new drugs are clinically more effective or have fewer side effects than existing treatments; however, Grabowski and Wang did not use data or studies of therapeutic outcomes. Instead, for example, they claim that global NCEs launched in four or more G7 industrialized countries are an "indicator of a drug's commercial and therapeutic importance." This confounds two quite different attributes.

Nexium and Lipitor, for example, are among the world's top-selling drugs, but Nexium is widely regarded as a textbook case of a me-too drug, and Lipitor has little proven clinical advantage over other statins.[13] Most new cancer drugs generate large revenues at high prices but have not proved to be clinically superior to existing ones.[14] Only 7 percent of new biotech products were proven clinically superior to comparator drugs in randomized trials.[15] In short, commercial success is often distinct from therapeutic importance.

The best evidence of clinical quality comes from systematic efforts to assess therapeutic advantage and adverse effects compared with existing drugs. A detailed analysis of therapeutic quality in new drugs over the past twenty years found that 14 percent of all new chemical entities are either therapeutic breakthroughs or substantially superior to existing medications.[16] Likewise, a comprehensive review of all new drugs approved between 1989 and 2000 in the United States concluded that 14.8 percent were new chemical entities that provided significant clinical improvement, and a Canadian review board concluded that 10.7 percent of new chemical entities in 2000–2004 did so.[17] During an earlier period, an often-cited industry assessment of all global NCEs in the 1970s and 1980s found that only about 11 percent of all new "international" drugs brought substantial new benefits to patients—a ratio of one in nine.[18] These figures are lower than the proportion of drug candidates given a priority rating by the U.S. Food and Drug Administration (FDA), because this rating is based on several criteria of promising benefits that might not always materialize.

Thus, different organizations, using somewhat different criteria and procedures, have found that during the past forty years about 11–15 percent of new chemical entities have been therapeutically "important," as Grabowski and Wang

"Lower European prices seem to be no deterrent to strong research productivity."

put it, and 85–89 percent have not been—a contrast with their using nontherapeutic criteria to conclude that 88.8 percent of all new chemical entities have been therapeutically important.

Policy Reflections

This study shows how data purporting to document how "U.S. firms overtook their European counterparts in innovative performance" actually document the greater and increasing research productivity of Europe. On the European side, a series of reports commissioned by the European Commission's Directorate-General for Commerce between 1993 and 2003 pronounced that the United States had eclipsed Europe in research productivity, despite little solid evidence.[19]

Congressional leaders and others concerned about high prices of new patented drugs will be heartened by this analysis, because lower European prices seem to be no deterrent to strong research productivity.[20] A previous analysis using industry-based data showed that pharmaceutical companies recover all costs and make a good profit at European prices.[21] Europeans are not "free riders" on American patients—another myth promoted by industry that assumes that countries are separate R&D/market silos that should each pay for themselves.

The real innovation crisis for patients and society is not the recent decline in new molecular entities but the small percentage over many years of new molecular entities that provide clinical advantages to patients over existing medications. This longer pattern stems from defining "effective" as better than placebo and using soft surrogate endpoints, or substitute criteria, instead of hard clinical endpoints.[22] As a result, the vast majority of new drugs that constitute 80 percent of U.S. pharmaceutical costs offer few therapeutic advantages and greater risks than good drugs discovered in prior years.[23] High prices for these new drugs enable companies to spend two and a half times more on marketing than on R&D, to persuade physicians to prescribe them and patients to want them.[24] Thus, current incentives reward better marketing more than better value.

If we want new drugs to be clinically superior to existing ones, we need to reward companies for developing them and not for developing drugs that are merely superior to placebo. Arjun Jayadev and Joseph Stiglitz propose a key strategy: pay in terms of clinical value added, as some large purchasers already do and as *Consumer Reports Best Buy Drugs* does by comparing value with price.[25] Jayadev and Stiglitz also recommend having clinical trials independently run and paid for by a public body such as the National Institutes of Health so that they can be designed to measure comparative advantages and risks over existing treatments. Publicly funded trials would also reduce cost and risk for pharmaceutical companies and

increase competition from smaller firms by lowering the high cost barrier that company-funded trials pose. These are some ways in which incentives can be restructured to foster greater competition for clinically superior drugs and to lower overall spending.

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NOTES

1. L. Gambardella, L. Orsenigo, and F. Pammolli, *Global Competitiveness in Pharmaceuticals: A European Perspective* (Brussels: Directorate General for Enterprise, European Commission, 2000); and High Level Group on Innovation and Provision of Medicines in the European Union, "Recommendations for Action" (Brussels: European Commission—Enterprise and Industry, 2002).
2. European Federation of Pharmaceutical Industries and Associations, *The Pharmaceutical Industry in Figures*, 2008 ed. (Brussels: EFPIA, 2008).
3. H.G. Grabowski and Y.R. Wang. "The Quantity and Quality of Worldwide New Drug Introductions, 1982–2003," *Health Affairs* 25, no. 2 (2006): 452–460.
4. IMS Health is the global leader in market intelligence and information on pharmaceuticals. See the IMS Health home page at http://www.imshealth.com.
5. Limitations of this analysis lie mainly in the original data. For example, assigning NCEs by where the launching company's headquarters was located is commonly used but is clearly less accurate than investigating where the real discovery and development took place. The first-in-class designation is the object of methodological debates discussed in the original article, but this reanalysis uses the count provided. Further limitations about research and development (R&D) investments also reside in the figures given. They cannot be verified and may include costs not reasonably considered R&D for new drugs. They may have been assembled by different trade associations in different ways. As in the original article, such limitations are accepted in order to focus on major trends using data presented by the industry.
6. Grabowski and Wang identified 659 global, first-in-class, biotech, and orphan NCEs out of their total 919 NCEs for both periods. Grabowski and Wang, "The Quantity and Quality."
7. Gambardella et al., *Global Competitiveness in Pharmaceuticals;* High Level Group, "Recommendations"; and U.S. Department of Commerce, *Pharmaceutical Price Controls in OECD Countries: Implications for U.S. Consumers, Pricing, Research and Development, and Innovation* (Washington: Department of Commerce, 2004).
8. S. Frantz, "Pharma Faces Major Challenges after a Year of Failures and Heated Battles," *Nature Reviews/Drug Discovery* 6, no. 1 (2007): 5–7.
9. EFPIA, *The Pharmaceutical Industry in Figures*, p. 4. I initially contacted Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington to ask for the best information on changes in industry R&D investments. The senior manager of policy, Gretta Thorn, sent me the EFPIA report as the best source. Extensive and ultimately unresolvable debates could be held about the consistency and quality of R&D funding reported by different companies to their trade association.
10. More finely grained analyses will run into the problem of small numbers for first-in-class, biotech, and orphan drugs.
11. Grabowski and Wang, "The Quantity and Quality," 452.
12. Top Institute Pharma creates collaborative academic and industry research teams involving several larger and smaller biotech companies, universities, and the Dutch government to accelerate commercial use of discoveries. For an overview, see D.J.A. Crommelin, "Public-Private Partnerships and 'Le Defi Americain' Revisited," *EUFEPS Newsletter* 15, no. 2 (2006): 1–3. The TI Pharma home page is http://www.tipharma.com. One of Europe's leading research institutes, Karolinska Institutet Innovations aims to develop commercial uses more fully before transferring technology through a licensing agreement to obtain more profitable terms. See its home page at http://www.karolinskainnovations.ki.se.Information on this large, complex European Innovative Medicines Initiative is available from Innovative Medicines Initiative, "Objec-

tives," http://imi.europa.eu/objectives_en.html (accessed 6 August 2009).

13. "Atorvastatin: Why Such a Commercial Success?" (editorial), *Prescrire International* 13, no. 74 (2004): 237; "Choix d'une Statine" (editorial), *La Revue Prescrire* 26, no. 276 (2006): 692–695; and P. Mansfield, D. Henry, and A. Tonkin, "Single-Enantiomer Drugs: Elegant Science, Disappointing Effects," *Clinical Pharmacokinetics* 43, no. 5 (2004): 287–290.
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15. R. Joppi, V. Bertele, and S. Garattini, "Disappointing Biotech," *BMJ* 331, no. 7521 (2005): 895–897.
16. "A Look Back at Pharmaceuticals in 2006: Aggressive Advertising Cannot Hide the Absence of Therapeutic Advances" (editorial), *Prescrire International* 16, no. 88 (2007): 80–86.
17. M. Hunt, *Changing Patterns of Pharmaceutical Innovation* (Washington: National Institute for Health Care Management Research and Education Foundation, 2002); and Patented Medicine Prices Review Board, *Annual Report 2004* (Ottawa: PMPRB, 2005).
18. P.E. Barral, *Twenty Years of Pharmaceutical Research Results throughout the World: 1975–94* (Paris: Rhone-Poulenc Rorer Foundation, 1996).
19. P. Stolk and D.W. Light, "Did the U.S. Eclipse European Research Productivity? An Analysis of Major Reports as Searchlights in the Fog," Report to TI Pharma Escher Project (Utrecht: University of Utrecht, 2008).
20. U.S. House Committee on Oversight and Government Reform, *Private Medicare Drug Plans: High Expenses and Low Rebates Increase the Costs of Medicare Drug Coverage*, http://oversight.house.gov/documents/20071015093754.pdf (accessed 6 August 2009); and U.S. Senate Committee on Finance, "Baucus Condemns Senate Failure on Medicare Drug Price Negotiation," Press Release, 18 April 2007, http://www.senate.gov/-finance/press/Bpress/2007press/prb041807a.pdf (accessed 6 August 2009).
21. D.W. Light and J. Lexchin, "Foreign Free Riders and the High Price of U.S. Medicines," *BMJ* 331, no. 7522 (2005): 958–960.
22. F.R. Curtiss and K.A. Fairman, "Looking for the Outcomes We Love in All the Wrong Places: The Questionable Value of Biomarkers and Investments in Chronic Care Disease Management Interventions," *Journal of Managed Care Pharmacy* 14, no. 6 (2008): 563–570.
23. M.K. Olson, "Are Novel Drugs More Risky for Patients than Less Novel Drugs?" *Journal of Health Economics* 23, no. 6 (2004): 1135–1158; D. Carpenter, E.J. Zucker, and J. Avorn, "Drug-Review Deadlines and Safety Problems," *New England Journal of Medicine* 358, no. 13 (2008): 1354–1361; and T.J. Giezen et al., "Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union," *Journal of the American Medical Association* 300, no. 16 (2008): 1887–1896. Patented drugs make up 28.7 percent of sales volume but 80.6 percent of costs. P.M. Danzon and M.F. Furukawa, "International Prices and Availability of Pharmaceuticals in 2005," *Health Affairs* 27, no. 1 (2008): 227, Exhibit 5.
24. A. Jayadev and J. Stiglitz, "Two Ideas to Increase Innovation and Reduce Pharmaceutical Costs and Prices," *Health Affairs* 28, no. 1 (2009): w165–w168 (published online 16 December 2008; 10.1377/hlthaff.28.1.w165). For *Consumer Reports Best Buy Drugs,* see http://www.consumerreports.org/health/best-buy-drugs/index.htm. Benefits, side effects, and costs are compared for thirty-five common conditions.