By Michael Lanthier, Kathleen L. Miller, Clark Nardinelli, and Janet Woodcock

An Improved Approach To Measuring Drug Innovation Finds Steady Rates Of First-In-Class Pharmaceuticals, 1987–2011

DOI: 10.1377/hlthaff.2012.0541
HEALTH AFFAIRS 32,
NO. 8 (2013): 1433–1439

ABSTRACT For more than a decade, industry analysts and policy makers have raised concerns about declining pharmaceutical innovation, citing declining numbers of new molecular entities (NMEs) approved in the United States each year. Yet there is little consensus on whether this is the best measure of "innovation." We examined NME approvals during 1987–2011 and propose the three distinct subcategories of NMEs—first-in-class, advance-in-class, and addition-to-class—to provide more nuanced and informative insights into underlying trends. We found that trends in NME approvals were largely driven by addition-to-class, or "me too," drug approvals, while first-in-class approvals remained fairly steady over the study period. Moreover, the higher proportion of first-in-class drug approvals over the most recent decade is an encouraging sign of the health of the industry as a whole.

Michael Lanthier (michael.lanthier@fda.hhs.gov) is an operations research analyst in the Office of Planning at the Food and Drug Administration (FDA), in Silver Spring, Maryland.

Kathleen L. Miller is a health economics doctoral student in the Department of Health Policy and Management at the University of North Carolina at Chapel Hill and an intern in the FDA Office of Planning.

Clark Nardinelli is the chief economist in the FDA Office of Planning.

Janet Woodcock is the director of the FDA Center for Drug Evaluation and Research.

Innovation in the pharmaceutical industry plays a vital role in improving public health. Major advances in the treatment of cardiovascular disease, infections, cancer, and a host of other medical conditions during the past five decades are attributable to new drug therapies.[1] Nevertheless, many serious illnesses lack effective therapies. Recent advances in basic biomedical science and resulting technologies, such as the use of genomics to personalize therapy to individuals, hold great promise for addressing unmet medical needs. An innovative pharmaceutical industry is critical to achieving this public health goal.

The conventional benchmark for measuring the pace of pharmaceutical innovation has been the total number of new molecular entities (NMEs) approved by the Food and Drug Administration (FDA) each year.[2–5] Generally, NMEs are considered to be chemically novel drugs and biologics that have not been previously marketed in the United States. The pace of NME approvals since 2000 has been sluggish, raising questions about the state of innovation in the pharmaceutical industry.[6,7] Given that investment in pharmaceutical research and development increased greatly over the same time period, this suggests a lower rate of return on investment and raises concerns about the health of the industry as a whole.[8,9]

However, measuring innovation based solely on the number of new drugs approved has considerable limitations. Although each NME is a chemically unique compound, a new entity could be similar in function and effectiveness to a drug already on the market or a major breakthrough in technology or treatment. To study truly innovative drugs approved since 1987, we proposed an improved approach for measuring innovation by defining three distinct categories of newly approved drugs. These categories separate drugs based on their degree of novelty compared to the existing base of pharmaceuticals. We determined whether an NME was the first drug approved in its class; whether it was a therapeutic advance within an existing drug class; or whether it was an addition to a drug class, providing only modest additional benefit relative to

other drugs. Using these definitions, we evaluated long-term trends in innovation during 1987–2011 to determine whether pharmaceutical innovation was really on the decline or whether the outlook was more favorable.

Study Data And Methods

Our preliminary data set encompassed novel drugs and therapeutic biologics regulated by the FDA Center for Drug Evaluation and Research (CDER) and approved by FDA during 1987–2011. Given our interest in novel therapeutic products, our data set excluded diagnostic drugs; drugs approved under an abbreviated regulatory pathway under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act; and products intended for use solely by US military personnel. These exclusions resulted in a defined subset of novel drugs similar to those used in related analyses.[2,5] Our final data set consisted of 645 NME approvals. (For a full list of drugs and classifications, see online Appendix Exhibit A.)[10]

We collected data on several attributes for each drug, including the active ingredient, trade name, the FDA approval date, and whether the drug received a "priority review" designation from FDA because it could offer a "significant improvement" compared with products already on the market. We also consulted the marketing approval letters that FDA sent to each pharmaceutical company to identify each drug's original approved use and the company that sponsored the marketing application.

We identified whether the marketing application was sponsored by a large or small pharmaceutical company. A firm was considered to be large if it was among the top twenty-five pharmaceutical companies based on total US sales revenues in the year the respective drug was approved, according to IMS Health sales data.[11] Although revenues are not a direct measure of a company's size, they are commonly used in rankings, with the highest revenues generated by large and well-established pharmaceutical companies. The remaining pharmaceutical companies were defined as small for purposes of this study, although some would be considered midsize for other purposes.

Our data may underrepresent the contribution by small companies in cases when a large company acquires a drug from a small company late in development, but we believe this to be a minor concern. By identifying the company receiving the FDA approval letter, our data are not distorted by situations where a large pharmaceutical company licenses and markets a drug approved from a small company and situations involving postapproval acquisitions.

DEFINING DRUG CLASSES Our objective in identifying drug classes was to group together drugs related in a clinically and pharmacologically meaningful way. For each drug in our data set, we identified the FDA established pharmacologic class (where available) and the drug's original approved indication, or use, to differentiate among drugs within a class that have different clinical uses.

The established pharmacologic class (for example, proton pump inhibitor, calcium channel blocker, and corticosteroid) is included within the FDA-approved drug labeling; it helps medical professionals understand the effects associated with a drug or members of a drug class. For a small number of drugs in our study (14 percent), we could not identify a documented established pharmacologic class. To find an appropriate term to represent the drug class in these instances, we referenced supplementary sources (for example, commercial databases, such as Drug Facts and Comparisons and Pharmaprojects) that track characteristics of prescription drugs, including pharmacologic and therapeutic class.[12,13]

After arriving at a preliminary set of drug classes and indications, we identified meaningful differences within drug classes that might merit further subclassification. For example, among several targeted cancer drugs classified as "kinase inhibitors," many work through different, but known, molecular pathways. We considered the specific molecular targets and indications to make further distinctions within this broad class.

Additionally, we enlisted the help of specialists and scientific staff at FDA to review and refine our drug class designations. Additional details on our drug classification approach are described in the Appendix.[10]

DEFINING INNOVATION CATEGORIES Key to our study was the definition of innovation categories. We found that although each NME is chemically distinct, not all NMEs are equally innovative. To classify NMEs by degree of novelty, we developed three categories: first-in-class, advance-in-class, and addition-to-class. We assigned each of the approved NMEs in our data set to one of these categories based on drug class, date of approval, and priority review determination.

The first drug approved within its respective drug class was deemed a *first-in-class drug*. First-in-class drugs are pharmacologically innovative because each represents a new pathway for treating a disease. Although subsequent approvals within the same class may prove to have advantages over the first drug, first-in-class drugs are genuinely innovative, because each represents a

novel approach to drug therapy.

Advance-in-class drugs were defined as drugs that were not first-in-class but received a priority review designation, which is reserved for medicines that potentially offer major advances in treatment. Priority review is granted only to marketing applications when the candidate therapy can differentiate itself from existing treatments in a clinically meaningful way. Priority review designation suggests a measurable degree of innovation in the clinical potential of a drug.

The remainder of drugs in the sample were classified as *addition-to-class drugs.* These drugs function similarly to other drugs in their class and do not offer substantial advantages in safety or efficacy over existing products. Addition-to-class drugs do represent additional options for patients and clinicians and may possess unique benefits and value for individual patients.[14] However, they generally represent a lower degree of innovation because at the time of FDA review, they did not distinguish themselves in terms of potential clinical benefit. Examples of drugs within our innovation categories are illustrated in Appendix Exhibit B.[10]

LIMITATIONS The determination of what constitutes a new class of drugs is, to some degree, subjective. However, we believe that our use of FDA-established pharmacologic class designations, approved indications, and supplementary sources served to minimize subjectivity and helped ensure that we applied our classification methodology in a consistent manner across the broad range of drugs studied.

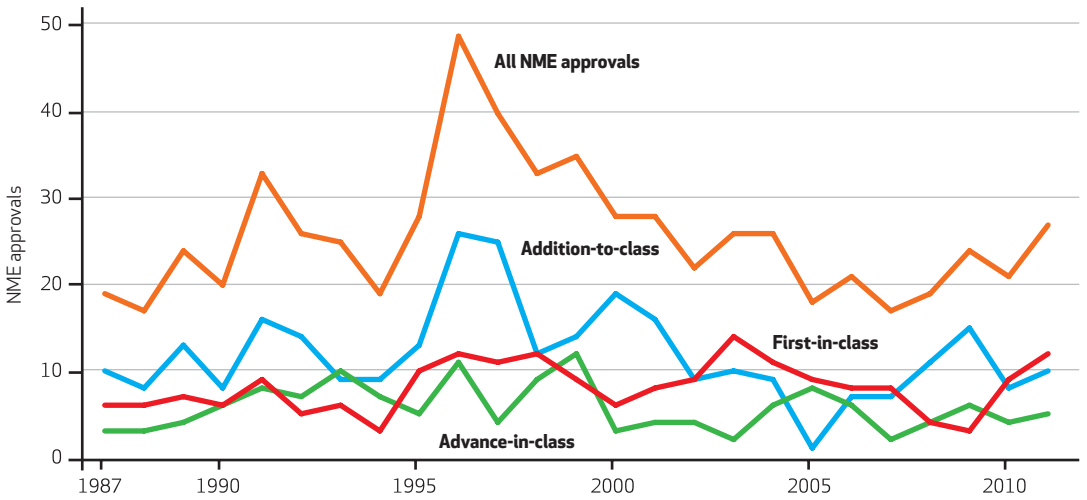
Similarly, there are inherent limitations in the use of "priority" versus "standard" review designations to distinguish between drugs within an existing class that represent major advances from additions to a drug class. Priority review designation is made before approval and is therefore a crude forecast of the ultimate clinical impact. As discussed below, because the scope of our analysis was limited to NMEs, we also failed to capture other ways in which pharmaceutical companies innovate, including, for example, incremental innovations that may occur through new formulations or new uses for existing drugs. We acknowledge that valuable innovations may indeed occur after the initial approval of a drug, but they are difficult to quantify. Regardless, the introduction of new molecular entities and new classes of drugs will always be a necessary first step that precedes any postapproval innovation.

Study Results

Exhibit 1 shows trends over the twenty-five-year period for all approved NMEs and across our innovation categories. Of the 645 drugs studied, 203 (32 percent) were first-in-class drugs, 143 (22 percent) were advance-in-class drugs, and 299 (46 percent) were addition-to-class drugs. The number of total approvals peaked in the mid-to-late 1990s, when approvals reached highs of forty-nine and forty new drugs in 1996 and 1997, respectively. Outside of this two-year peak, the average number of NME approvals has remained around twenty to thirty approvals per year. Although some observers note that approvals have declined since 1996, the twenty-five-year data suggest that the high number of approvals

EXHIBIT 1

New Molecular Entity (NME) Approvals, By Innovation Category, 1987–2011



SOURCE Food and Drug Administration drug-approval data. **NOTE** Innovation categories are defined in the text.

in 1996 and 1997 marked an exceptional period of increased approval activity, sometimes attributed to a 50 percent increase in FDA drug review staff following passage of the Prescription Drug User Fee Act of 1992.[9,15]

INNOVATION SUBCATEGORIES Although the number of NME approvals per year is a common benchmark measure of pharmaceutical innovation, we argue that the innovation subcategories described in this article provide more nuanced and informative insights into underlying trends. Using these categories, we found that variations in the number of addition-to-class drug approvals largely drove the trends in drug approvals during the study period, including the spike and subsequent decline in approvals in the mid-to-late 1990s (Exhibit 1). In other words, changes in the number of new drugs not considered substantial therapeutic advances (that is, less innovative for the purposes of this study) account for most of the annual variation in the total number of approved NMEs.

We identified 299 addition-to-class drugs, representing 135 distinct drug class categories. Of note, 60 percent (135) of the addition-to-class approvals were concentrated in just thirty-five drug classes, where addition-to-class drug approvals were more common (that is, there were three or more addition-to-class drugs in the class). Among these classes were cephalosporin and fluoroquinolone antibiotics (twenty-five addition-to-class drugs within these two classes) and angiotensin-converting enzyme inhibitors, angiotensin-2 receptor blockers, calcium channel blockers, and beta-blockers to treat high blood pressure (twenty-seven addition-to-class drugs across these four classes). In general, drug categories with many addition-to-class drug approvals tended to encompass drugs for chronic conditions, such as diabetes; drugs to treat conditions that affect large patient populations, such as bacterial infections; or both.

First-in-class drug approvals, however, represent a moderate and fairly steady source of annual approvals. The number of first-in-class drugs remained remarkably stable over twenty-five years, with an average of roughly eight new first-in-class drugs per year. One exception was the appreciable drop in first-in-class approvals in 2008 and 2009, for reasons that remain unclear. These numbers recovered and increased in 2010 and 2011, with nine and twelve first-in-class approvals, respectively.

First-in-class drugs in our sample tended to be for serious and life-threatening conditions, including cancer (thirty-two first-in-class approvals); rare genetic disorders, such as inherited metabolic storage disease, hereditary angioedema, and cystic fibrosis (nineteen approvals); and neurodegenerative conditions, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease (eleven approvals). Some first-in-class approvals ushered in a wave of new treatments, with multiple drugs following the innovator. For instance, in the first year of our study data (1987), pioneering drugs included Retrovir, the first drug approved to treat HIV; Mevacor, the first "statin" to lower cholesterol; and Prozac, the first selective serotonin reuptake inhibitor antidepressant.

Advance-in-class drugs also have the potential to provide major advances in the treatment or prevention of disease, although addition-to-class drugs provide an alternative product but no substantial new medical benefit. Exhibit 1 shows that advance-in-class drugs account for a small proportion of the year-to-year variation in approvals. As with first-in-class drugs, we found that advance-in-class drugs tend to focus on treatments for serious conditions, with more than one-third of advance-in-class drugs treating cancer or HIV.

Although the share of addition-to-class approvals has fallen in recent years, there has been an increased share of first-in-class approvals in the most recent decade. First-in-class drugs made up 39 percent of total approvals during 2002–11, compared to only 27 percent of total approvals over the fifteen preceding years.

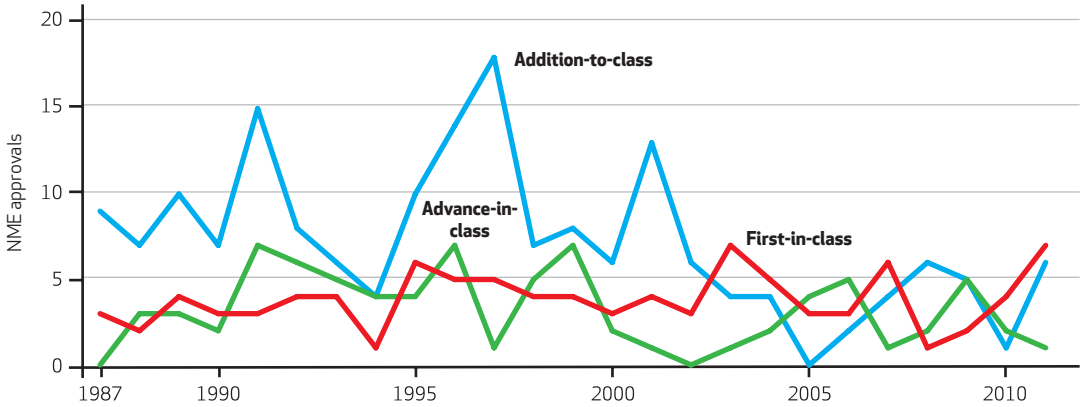
LARGE VERSUS SMALL COMPANIES The pharmaceutical industry has evolved greatly in the past decades, with industry consolidation accompanied by the emergence of smaller biotechnology companies.[16] To explore the possible effects of this evolution on innovative drug development, we compared approval trends for large and small pharmaceutical companies. Broadly, we found that NME approvals were split fairly evenly, with 45 percent of approvals attributable to small companies and 55 percent to large companies. Analysis across our innovation subcategories, however, showed that despite fewer NME approvals overall, small companies developed a slightly larger percentage of first-in-class drugs (53 percent) and only 40 percent of all addition-to-class drugs. Exhibits 2 and 3 show approvals within these innovation categories based on company size.

Since 1987, large and small pharmaceutical companies have produced first-in-class drug approvals at similar and stable rates. Both segments of the industry have averaged roughly four first-in-class drug approvals per year, with no substantial upticks or decreases in first-in-class approvals over time.

We further evaluated trends in approvals both before and after the surge in approvals in 1996 and 1997 and found striking differences in the

EXHIBIT 2

New Molecular Entity (NME) Approvals For Large Pharmaceutical Companies, By Innovation Category, 1987–2011



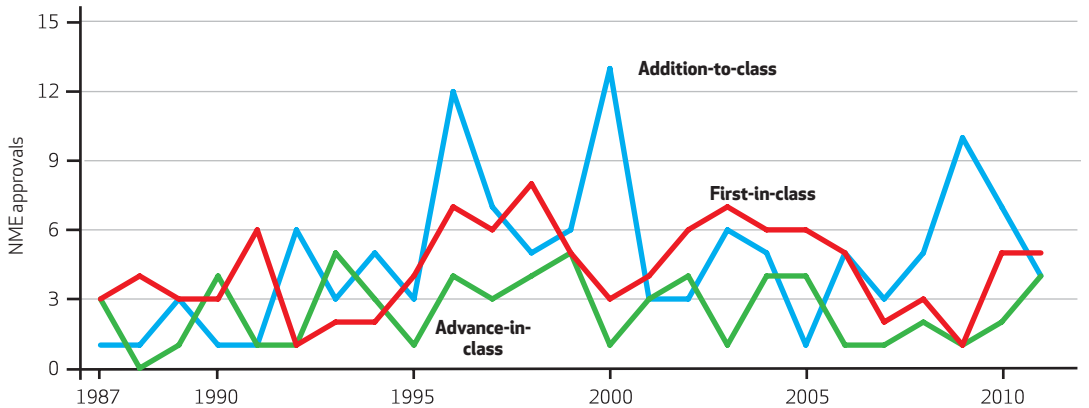
SOURCE Food and Drug Administration drug-approval data, IMS Health. **NOTES** Innovation categories are defined in the text. Large companies are those in the top twenty-five in US sales revenue in a specified year based on IMS Health sales data. All other companies are considered to be small companies.

innovative characteristics of drugs developed by small versus large companies. During the nine-year period before approvals peaked during 1996–97, the majority of new drugs from large pharmaceutical companies were addition-to-class drugs, while drug approvals from small pharmaceutical companies were more likely to be first-in-class and advance-in-class drugs by a ratio of nearly two to one. Although large companies accounted for nearly double the number of drugs approved between 1987 and 1995 (large companies introduced 140 NMEs, while small companies introduced only 71), large and small companies produced roughly the same number of first-in-class drugs (30 for large, 28 for small companies).

Beginning in 1996, NME approvals from small companies increased notably. Before 1996, small companies contributed an average of fewer than eight NME approvals per year. In 1996, the number surged to twenty-three approvals, largely because of new addition-to-class drugs. In subsequent years, NME approvals from smaller firms remained at increased levels—more than doubling to an average of nearly eighteen drug approvals per year during 1997–2000. During 1996–2011, small companies accounted for 50 percent of NME approvals, compared to roughly one-third of drug approvals before the observed surge. The reason for this trend re-

EXHIBIT 3

New Molecular Entity (NME) Approvals For Small Pharmaceutical Companies, By Innovation Category, 1987–2011



SOURCE Food and Drug Administration drug-approval data, IMS Health. **NOTES** Innovation categories are defined in the text. Small companies are those outside the top twenty-five in US sales revenue in a specified year based on IMS Health sales data. All other companies are considered to be large companies.

mains unclear, although the data suggest the emergence of smaller companies as drivers of novel drug development.

Following the peak approval years of 1996 and 1997, the number of addition-to-class approvals generally declined for both large and small companies through 2005. During 2002–11, large and small companies generally seemed to shift away from addition-to-class drug development.

Policy Implications

A number of initiatives were launched during 2002–11 to foster innovation in drug development.[17] More recent statutory and regulatory policy efforts are reinforcing this push. Thus, our observations may be of interest to policy makers as a baseline and method against which the success of these initiatives can be measured.

Of the first-in-class drugs we identified, 70 percent received a priority review rating, meaning that FDA deemed these products to be potentially substantial advances relative to existing therapies. But innovation does not end with the introduction of a first-in-class drug, as the pioneering therapy is often followed by related products that still offer innovative advances in safety and efficacy within the class. Consistent with findings in other studies, our study showed that of the 442 drugs in our data set that were not considered first-in-class, 32 percent received priority review designation.[18]

There are a number of possible explanations for the drug development trends we observed. Before 1996, large and small companies contributed differently to the mix of approved NMEs: The majority of NMEs from large companies were addition-to-class approvals versus primarily first-in-class and advance-in-class drugs coming from small companies. Drug classes that attracted multiple addition-to-class approvals tended to be those that treated chronic conditions in large patient populations. These data are consistent with the view that for a period of time, the pharmaceutical industry was actively engaged in developing drugs to compete in large and potentially lucrative markets, with the goal of developing a "blockbuster" drug that would generate high sales revenues.[8]

Today we see a trend away from addition-to-class drugs and an increased focus on first-in-class drugs. Although we can only speculate about the causes for this shift, one possible reason deserving of more attention may be the influence of large pharmacy benefit management firms—third-party administrators that process prescription drug claims. These firms, which negotiate discounts with pharmaceutical manufacturers and maintain formularies, may be less willing than other payers to reimburse for highly priced addition-to-class drugs that cannot demonstrate a proven benefit over similar products already on the market. Such decisions could make it less attractive for companies to develop addition-to-class drugs once multiple drugs have established themselves on the market.[19–21] This shift may also be a natural consequence of an exhaustion of available "low-hanging fruit," or diminishing room for competitors in an already crowded market.[22] In any case, as drug candidates compete for the same pool of available research and development dollars, decreased investment in addition-to-class drugs likely translates to more industry resources available for research into more-innovative new drugs.

Policy makers at the federal level continue to express their concerns about the state of pharmaceutical innovation, especially in certain therapeutic areas of great need, such as antibiotic-resistant infection and rare pediatric disease. The FDA Safety and Innovation Act of 2012 includes provisions to incentivize antibiotic development (through the Generating Antibiotic Incentives Now Act of 2011) and establishes a new breakthrough designation program for highly promising investigational drugs. Under the FDA Safety and Innovation Act, FDA also must expand the scope of products eligible for accelerated approval, allowing for approvals based on surrogate endpoints, which are not clinical endpoints but are reasonably likely to predict clinical benefit. In addition, the President's Council of Advisors on Science and Technology issued a 2012 report on pharmaceutical innovation containing an ambitious plan for spurring development, including increasing funding and support for biomedical research, expanding expedited drug-approval mechanisms for drugs addressing unmet medical needs, and studying economic incentives to promote innovation in areas of high public health importance.[23] These various efforts should have an impact on innovation in drug development during the coming decades. To be able to track the success of these and other initiatives, however, methods for assessing medically meaningful innovation, such as those proposed here, will surely be needed.

Conclusion

Pharmaceutical innovation will be critical to advancing the treatment of the many diseases that still lack effective therapies. When we categorize new drug approvals in a way that recognizes important differences in the novel contribution of a drug, we find that the pace of approvals of pioneering first-in-class drugs has

remained relatively stable over time. This is encouraging news. However, simply maintaining a stable output of novel new drugs may not be sufficient to sustain today's pharmaceutical industry, given the increasing costs and complexities of drug development. For this reason, many efforts are under way to foster innovative drug development, including a number of federal initiatives. A strong and innovative pharmaceutical industry must continue to be an important public health goal, and the sophisticated measurement of innovation will be imperative in tracking the progress being made. ■

NOTES

1 Lichtenberg FR. Pharmaceutical innovation, mortality reduction, and economic growth. Cambridge (MA): National Bureau of Economic Research; 1998. (Working Paper No. 6569).
2 Grabowski HG, Wang YR. The quantity and quality of worldwide new drug introductions, 1982–2003. Health Aff (Millwood). 2006;25(2):452–60.
3 Light DW. Global drug discovery: Europe is ahead. Health Aff (Millwood). 2009;28(5):w969–77. DOI: 10.1377/hlthaff.28.5.w969.
4 Kola I. The state of innovation in drug development. Clin Pharmacol Ther. 2008;83(2):227–30.
5 DiMasi JA. New drug innovation and pharmaceutical industry structure: trends in the output of pharmaceutical firms. Drug Inf J. 2000;34(4):1169–94.
6 Kaitin KI, DiMasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000–2009. Clin Pharmacol Ther. 2011;89(2):183–8.
7 Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010;9(3):203–14.
8 Cockburn IM. Is the pharmaceutical industry in a productivity crisis? Chapter 1 in: Jaffe AB, Lerner J, Stern S, editors. Innovation policy and the economy. Volume 7. Cambridge (MA): MIT Press; 2007. p. 1–32.
9 Munos B. Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov. 2009;8(12):959–68.
10 To access the Appendix, click on the Appendix link in the box to the right of the article online.
11 US sales data for the top twenty-five pharmacuetical companies are from three IMS Health publications: for 1980–86, "US Pharmaceutical Market: Drug Store and Hospital Purchases (January–December)"; for 1997–2000, "Retail Perspective and Provider Perspective (January–December)"; and for 2001–10, "National Sales Perspectives: Retail and Non-Retail Combined Report (January–December)."
12 Drug facts and comparisons [proprietary online database]. St. Louis (MO): Wolters Kluwer Health; 2007.
13 Pharmaprojects [proprietary online database]. Richmond (UK): PJB Publications; 2007.
14 Wertheimer AI, Levy R, O'Connor TW. Too many drugs? The clinical and economic value of incremental innovations. Chapter 4 in: Farquhar I, Sorkin A, Summers K, editors. Research in human capital and development: investing in health: the social and economic benefits of health care innovation. Volume 14. Greenwich (CT): JAI Press; 2001. p. 77–118.
15 Food and Drug Administration. White paper: Prescription Drug User Fee Act (PDUFA): adding resources and improving performance in FDA review of new drug applications [Internet]. Silver Spring (MD): FDA; 2005 [last updated 2010 May 3; cited 2013 Jun 27]. Available from: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119253.htm
16 Cockburn IM. The changing structure of the pharmaceutical industry. Health Aff (Millwood). 2004;23(1):10–22.
17 Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products. Silver Spring (MD): FDA; 2004.
18 DiMasi JA, Paquette C. The economics of follow-on drug research and development. Pharmacoeconomics. 2004;22(2):1–14.
19 Murray MD, Deardorff FW. Does managed care fuel pharmaceutical industry growth? Pharmacoeconomics. 1998;14(4):341–8.
20 Gassmann O, Reepmeyer G, Von Zedtwitz M. Leading pharmaceutical innovation: trends and drivers for growth in the pharmaceutical industry. Berlin: Springer; 2008.
21 Pammolli F, Riccaboni M. Market structure and drug innovation. Health Aff (Millwood). 2004;23(1):48–50.
22 Cohen FJ. Macro trends in pharmaceutical innovation. Nat Rev Drug Discov. 2005;4(1):78–84.
23 President's Council of Advisors on Science and Technology. Report to the president on propelling innovation in drug discovery, development, and evaluation. Washington (DC): PCAST; 2012.