

Here I describe some of the findings that support these conclusions, focusing only on macro trends in major pharmaceutical industry innovation and avoiding anecdotes concerning specific innovations. The discussion is organized into two parts. In the first part, trends in industry's capacity for (also called commitment to) innovation are described, and in the second, trends in the industry's innovative output.

Defining innovation

According to the US Office of Technology Assessment (OTA), "Innovation encompasses both the development and application of a new product, process, or service. It assumes novelty in the device, the application, or both. Thus, innovation can include the use of an existing type of product in a new application or the development of a new device for an existing application. Innovation encompasses many activities, including scientific, technical, and market research; product, process, or service development; and manufacturing and marketing to the extent they support dissemination and application of the invention."²

As referred to here, innovation usually means the outcome itself — the actual creation or invention, and not just the process. Processes and resources that contribute to innovation are described as such. The phrase 'incremental innovation' denotes innovations that are improvements, from modest to major, on existing innovations. Incremental innovations are sometimes referred to as sequential, subsequent or follow-on innovations. In the pharmaceutical industry specifically, the modification of existing medicines — for example, by re-formulation — is often referred to as sequential innovation, whereas a second- or third-generation product in a chemical class is often referred to as a follow-on innovation. Critics dispense with these formalities and refer to any drug that is not pioneering as a 'me-too', a tactic obviously intended to denigrate the practice of incremental innovation. Pioneering innovations, which are also referred to as major, stand-alone, discontinuous or radical, usually describe the subset of innovations that represent something completely new and different. In pharmaceuticals, pioneering innovations are first-in-class drugs, although some critics also label first-in-class drugs that are similar to those in existing classes as 'me-too'.

Importance of incremental innovation

In its comprehensive report on commercialization of emerging technologies, the OTA concluded that "In most industries, innovation proceeds in an evolutionary fashion

OPINION

Macro trends in pharmaceutical innovation

Fredric J. Cohen

Abstract | Critics decry the lack of 'truly innovative' new medicines and question the role of the pharmaceutical industry in creating the few that are developed.

Is this an accurate portrayal of the state of pharmaceutical innovation? Does major pharma still innovate? If so, how? Must the industry innovate to survive? These and related issues are discussed.

Employees in the pharmaceutical industry have become accustomed to reading criticisms of their work in the lay press. Some of that criticism is, no doubt, deserved. But what about the charge that the pharmaceutical industry, particularly major pharma, is no longer innovative? This is not a new claim, but it is being recycled and has recently featured prominently in the media. The indictment usually takes this form: the pharmaceutical industry does not innovate much, as it has little incentive to innovate. Very few new drugs are truly innovative; most are

'me-toos'. The few truly innovative drugs were mostly discovered using government funds (BOX 1).

The truth is that there are no generally accepted measures of innovation that would conclusively prove the point one way or another (BOX 2). However, the current analysis identifies trends in several measures that support both sides of the innovation debate. Overall, though, the bulk of evidence suggests, to this admittedly biased observer, that the pharmaceutical industry continues to regard pioneering innovations as important, as evidenced by the motivation, effort and ability of the industry to create such innovations. However, like other mature manufacturing industries, the pharmaceutical industry relies heavily on incremental innovations (what critics call 'me-too' drugs) to sustain its profits¹. To a large extent, these incremental innovations are themselves medically beneficial and should be encouraged, rather than dismissed as merely imitative.

Box 1 | Whose drug is it anyway?

Some critics charge that the pharmaceutical industry is not primarily responsible for medical innovations, because they are the fruits of indirect — and frequently direct — involvement of researchers in academia and government-supported laboratories. But that is not what US government studies indicate, as the following excerpts demonstrate:

“Pharmaceutical innovation has resulted primarily from the activities of private industry. Of the new drugs introduced in the United States between 1960 and 1969, 91 percent were discovered and developed by the industry. Government, nonprofit research organizations, and universities were responsible for the remainder of the new drugs.”¹⁵

“It is important to note that while NIH’s federally funded research has contributed in a substantial, dramatic, yet general, way to advances in medicine and biology, the direct contributions to a final therapeutic product as a consequence of the Bayh-Dole process is limited and difficult to determine ... For each drug listed, NIH sought to determine whether the agency, directly, or through a grantee or contractor, held any patent rights to the drugs. From the comprehensive cross-analysis of all 47 [top-selling] drugs, it was determined that NIH has Government use or ownership rights to patented technologies used in the development of four of those drugs. Those four are Taxol, Epogen, Procrit, and Neupogen.”²⁷

“Even in those few cases in which an NIH-invented technology is an identifiable part of a final product, the invention would typically be one of numerous components... The research supported and conducted by the NIH is sometimes mischaracterized as necessarily resulting in the commercialization of drug products. In truth, much of NIH funding supports the exploration of fundamental biological mechanisms that would otherwise not be pursued due to the lack of market incentives ... [O]f the top 100 pharmaceuticals procured by the Department of Veterans Affairs in fiscal year 2001, only five implicated Government rights. Additionally, of the top 100 pharmaceuticals dispensed by the Department of Defense between July 1, 2001 and June 30, 2002, only three had active Government right.”²⁸

therefore an important source of R&D funds. If policy changes dry up the flow of incremental innovations — and in the absence of an alternative mechanism for replenishment — the R&D well will inevitably run dry and, along with it, the resolve of this industry to pursue pioneering innovations.

Motivations to innovate

Pharmaceutical proponents generally suggest that the industry is primarily motivated to create two things: drugs that serve society and drugs that serve investors. Critics begrudge these proponents their first point; so, for the sake of argument, let us just assume that the industry is motivated by profits alone, without concern for the welfare of society. Do profits alone serve as an incentive for innovation in general? The answer, as provided by studies unique to the pharmaceutical industry⁶ and to manufacturing industries generally², is an unequivocal ‘yes’. Profits are directly related to R&D investment^{1,7}, appropriation of inventions (for example, patents) and to innovative products themselves². The reasons for this are primarily two-fold: innovations improve sales, both in terms of volume⁸, by expanding the population being treated, and price⁹. Process innovations further improve profits by reducing costs relative to output¹⁰.

The competitive environment for new drugs has shifted in the past 20 years, causing increased pressure on innovator firms to ‘innovate or die’. Because of changes in federal and local laws in the 1980s that increased the availability and encouraged the use of generic medicines, generic competition is now much stiffer than prior to this time. Generic competition erodes innovator drug profits by reducing revenues owing to reductions in

through long periods of cumulative incremental innovation punctuated by moments of radical innovation. Although incremental innovation and adaptations of existing technology to new markets might seem mundane, they account for most innovative activity and, in aggregate, generate returns equal to those created by less frequent radical innovations.”²²

Speaking specifically about pharmaceutical innovation, the US National Research Council noted that “breakthrough products, which are usually the first of a class, inevitably display deficiencies after they are widely distributed. Pharmaceutical companies use these revealed deficiencies as opportunities to develop related compounds that are more effective, more selective, and less toxic”³. A more recent McKinsey study concurs with these observations: “Of the 32 such drugs introduced over the past decade, only a quarter targeted novel mechanisms of action ... Some of these were ‘me-too’ compounds, but a majority had at least one source of significant clinical differentiation...”²⁴.

As Wertheimer and colleagues have observed, “The therapeutic power, stability, and utility of a [drug] class are defined through the contributions of its multiple agents ... [therefore,] the collective therapeutic advantage of the class as a whole may be of greater clinical significance than the original advantage of the pioneer compound.”²⁵

Ironically, the radical innovation collectively described as ‘personalized medicine’ is dependent on incremental innovations — in the form of expansions in the members of each drug class. Offering choices requires choices to offer.

Finally, whether one accepts evidence pointing to the medical and social importance of incremental innovations or not, such innovations are an important source of industry revenues and profits because of their inherently lower risk and cost basis, and are

Box 2 | Innovation metrics: quality versus quantity

Assessing the quantity of innovation is relatively easy compared with measuring quality. Industry critics have proposed schemes for lumping together innovations into buckets and labelling them (for example, ‘highly innovative’, ‘moderately innovative’ and so on), sometimes using the FDA’s assessment of a drug’s therapeutic potential at the time of New Drug Application filing. But this approach is far from reliable and is just as subjective as selective as anecdotal descriptions of innovations. A few examples illustrate this point — in the following, which drug in each pair is more innovative?

A reformulation of an existing cytotoxic chemotherapy that allows it to be delivered at a higher concentration over a longer duration, resulting in longer disease-free survival and reduced toxicity compared with the original formulation; or, a novel, fast-tracked, priority-reviewed New Molecular Entity (NME) that was designed to supplant the original cytotoxic and demonstrates survival improvements and toxicities comparable to that of the reformulated cytotoxic?

A first-in-class, priority-rated NME with identical indications for usage, and indistinguishable safety and efficacy markers, as the first four members of an older drug class; or, a fifth-in-class NME that has been demonstrated to improve survival, when its four predecessors were not studied adequately to ascertain their effects on survival?

A combination of two older drugs that has been shown to have a heretofore unexpected benefit to treat a serious disease for which neither was previously studied; or, a novel, fast-tracked, priority-reviewed NME that has comparable efficacy and safety to the combination of the two older drugs?

both volume and price¹¹. For example, a 1993 study by the OTA found that a 43% erosion of innovator-drug sales (measured by volume, not price) occurred over 3 years for generic

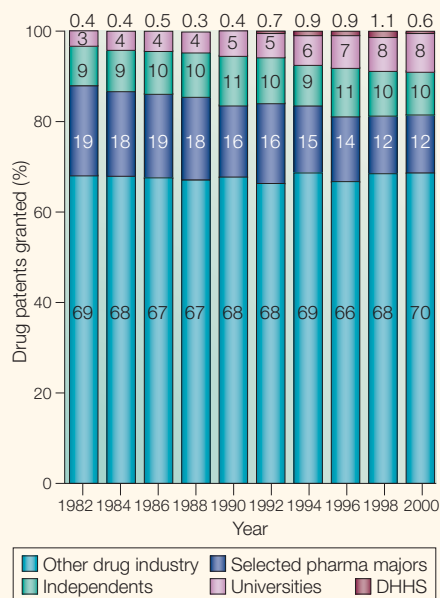


Figure 1 | Distribution of drug patents by assignee 1982–2000. Data are from searches of the US Patent and Trademark Office (USPTO) database in September 2004 and from USPTO’s Patent Technology Monitoring Division²⁵. The USPTO assigns each utility patent (a category that includes, for example, composition of matter, crystal form, formulation, and methods of manufacture and administration) a classification code according to how it will be used. For example, there are two classification codes for “drugs and bio-affecting and body treating” inventions. Patents from these classes are highly correlated with those that are discovered via searches for the term ‘pharmaceutical’ in the claims of patents ($R^2 = 0.98$). Light blue columns represent issued US patents classified as ‘drugs’ as a percentage of utility drug patents issued during the labelled year that were assigned to drug companies, excluding those in the major pharma cohort (included: Abbott Laboratories, AstraZeneca, Aventis, Ciba-Geigy, Eli Lilly, Hoechst Aktiengesellschaft, Hoechst Marion, Hoffmann-La Roche, Imperial Chemical Industries, Marion Laboratories, Marion Merrell, Merck & Co., Bristol-Myers Squibb, Merck Patent, Novartis, Pfizer, Rhone-Poulenc, Roussel-Uclaf, Sandoz Ltd., Sandoz Pharm., Schering Aktiengesellschaft, Schering Corp., Schering-Plough, Takeda Chemical, Warner-Lambert, Zeneca Limited). Note that light blue columns were obtained by deducting the contributions of all other assignee categories from the total. Other columns were for utility drug patents assigned to the following categories: blue, major pharma; green, independent (unaffiliated); pink, university or college; red, US Department of Health and Human Services (DHHS; includes National Institutes of Health, Food and Drug Administration and Centers for Disease Control).

drug introductions in the period 1984–1987¹². Just 6 years later, a US Congressional Budget Office study found that market erosion by generic competitors was 44% after the *first year* of generic competition for generics introduced between 1991 and 1993⁹. The innovator market had therefore eroded at least three times faster during this interval⁹. As a result, the volume share of generic prescription drugs has increased from 19% to 45% between 1984 and 2001¹³.

It has been argued that generic competition alone does not serve as an incentive to innovate, because companies can respond by creating more drugs with minor modifications (more me-toos). There is a problem with this argument, however, because it does not account for how the industry actually generates returns on its R&D investments, which in the pharmaceutical industry are highly skewed: the top 10% of new drugs (by net present value (NPV)) account for 52% of the total NPV for all new drugs sold worldwide¹⁴. Because utility is the primary driver of new drug adoption, profits could actually fall unless the quality of some new drugs is sufficient to compete effectively with older drugs. In other words, a pharmaceutical company must have a blockbuster every so often to keep returns growing. Therefore, increasing production of new drugs *per se* will not guarantee that profits grow at a pace sufficient to cover the uncertainty and costs of maintaining a drug pipeline. It follows from this line of reasoning that targeting the best-selling drugs — for example, with restrictive reimbursement, or regulatory or patent policies — can adversely affect innovation¹¹.

The industry’s capacity for innovation

Patents. The pharmaceutical industry relies heavily on patents to appropriate its innovations, perhaps more heavily than any other industry^{6,10,11}. As the OTA has described, “Patents were designed to promote innovation by providing the right to exclude others from making, using, or selling an invention. They enable innovators to obtain greater profits than could have been obtained if direct competition existed. These profits act as incentives for innovative activities”¹⁵. A US Federal Trade Commission survey recently concluded that “pharmaceutical companies ... rely on patents to prevent free riding, recoup their R&D investments, and learn about new technological breakthroughs”¹⁰. Also, “by requiring public disclosure of new inventions, the patent process ... encourages dissemination of new technical information”²². Given the importance of patents to the pharmaceutical enterprise, it is unlikely that companies would develop

innovations without them, and so they should be good surrogates of innovation capacity. On the other hand, there are incentives for companies to delay patent filings as long as possible (to lengthen the effective patent life during marketing) and to file multiple patents around the same fundamental technology to provide maximal protection against competitors. These incentives make patents an imperfect metric of innovation capacity.

Changes in US patent law in the mid-1980s (specifically the Hatch–Waxman Act) seem to have had, overall, a neutral effect on the industry’s incentives to innovate. On the one hand, Hatch–Waxman increased average effective patent life from about 10 years to about 12 years¹¹. On the other hand, anecdotal evidence suggests that improvements in technology have allowed ‘fast followers’ to follow faster than before¹⁶. These two trends have tended to counteract each other in terms of aggregate return.

US pharmaceutical patent activity, relative to overall US patent activity, increased beginning in the mid-1990s. Before then, it had been stable, at least as far back as 1976 (data not shown). The increase in activity seems to have been largely due to an increase in biotech-related patenting rather than an increase in patents on small-molecule drugs¹⁷ (data not shown). Consistent with this notion, increased drug patent activity seems to be largely due to an increase in patenting by universities and colleges; patent activity by a cohort of major pharmaceutical companies decreased relative to other assignees during this period (FIG. 1). The finding of relatively reduced drug patenting by the majors is consistent with the observations by McGahan and Silverman that, as industries mature, their leaders tend to diversify their patent output beyond the industry’s original activities¹⁸. The current study did not track patenting in areas in which these industry leaders might have diversified their efforts, such as research technologies, medical devices and clinical diagnostics.

R&D. The pharmaceutical industry spends more on R&D as a percentage of gross output than any industry except aerospace¹⁹. Pharmaceutical industry R&D expenditures (unadjusted for gross domestic product (GDP)), as reported yearly in the **Pharmaceutical Research Manufacturers of America** (PhRMA) Annual Survey, increased exponentially from 1970 to 2001, with some evidence of a moderation of spending growth more recently (FIG. 2a). It should be noted that these figures represent both pre- and post-approval R&D expenditures. When spending

is reflected as a percentage of net sales, a different picture emerges. R&D as a percentage of sales was stable until the latter half of the 1970s and then increased linearly until the mid-1990s, when it initially stabilized and then began diminishing slightly (FIG. 2a). So, although the industry was enthusiastically returning an increasing proportion of its revenues to R&D throughout much of the past 30 years, it now seems to be less inclined to do so.

R&D spending by the pharmaceutical industry was compared with other industries using the National Science Foundation Survey of Industrial Research and Development²⁰ as the data source (FIG. 2b). Although the actual R&D spending and sales amounts are different between the PhRMA and NSF surveys, the patterns of spending and sales over time are similar. Pharmaceutical industry R&D as a percent of sales peaked in the 1990s after a run-up in the 1980s, and has since plateaued at around 10%. Pharmaceutical industry R&D as a percentage of sales has exceeded aggregate industry R&D spending by a two-to-one margin since at least the late 1950s, when this survey began. Pharmaceutical industry R&D increased further relative to other industries beginning in the early 1960s (perhaps in response to US regulatory changes that called for clear demonstrations of efficacy and safety prior to marketing approval). Throughout the 1970s and early 1980s, pharmaceutical R&D spending generally exceeded aggregate industry spending by a ratio in excess of three to one. Following this period there was a brief lull in relative R&D spending by the pharmaceutical industry, followed by a surge in 1993 and then a return to the relative strength of the 1970s period.

The way in which R&D expenditures have been apportioned were examined by returning to the NSF Survey of Industry, which periodically collected information on pharmaceutical industry spending from 1965 to 1999 in three categories: basic, applied and development. Throughout this 34-year period, the allocation of pharmaceutical industry R&D expenditures gradually shifted away from applied research and towards development, with basic research remaining relatively stable (data not shown). Development accounted for more than 60% of R&D expenditures in 1999.

The annual PhRMA survey also collected data on the allocation of R&D funds, the findings of which are summarized in FIG. 3. Since 1976, the pharmaceutical industry has allocated relatively more funds to clinical research (Phases I–IV) and regulatory functions, at the expense of preclinical research. Together, these three categories accounted for

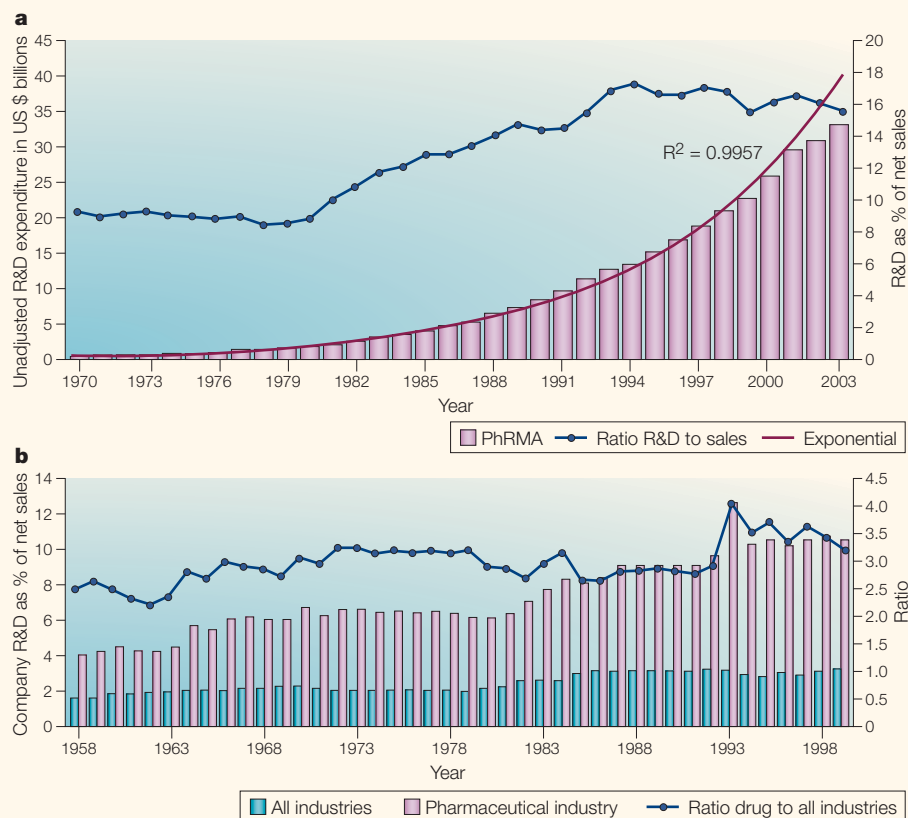


Figure 2 | Pharma R&D spending. **a** | Pharmaceutical industry R&D spending 1970–2003. Pink columns represent unadjusted annual R&D expenditures of Pharmaceutical Research Manufacturers of America (PhRMA) member companies as reported in their annual surveys. Spending is as reported, unadjusted for gross domestic product. An exponential curve (red) has been fitted to these data along with the square of the correlation coefficient. The blue curve represents annual R&D expenditure as a percentage of net sales. Source: REF. 26. **b** | Pharmaceutical industry R&D spending compared with aggregate industrial R&D spending 1958–1999. Light blue columns represent annual R&D expenditures expressed as a percentage of net sales for the aggregate of all industries represented in the National Science Foundation Annual Survey of Industrial Research and Development²⁰. Pink columns are data from the same surveys from just the pharmaceutical manufacturers (US Standard Industrial Classification 283). The blue curve represents the ratio of annual pharmaceutical R&D spending to aggregate industrial R&D spending.

55% of all R&D expenditures in 2002. PhRMA member companies also indicated that approximately 20% of domestic R&D spending — which was stable throughout the time interval examined — was allocated to projects that represented sequential innovations to drugs already developed (not shown).

Combining the PhRMA surveys' findings with those from the NSF surveys suggests that applied non-/preclinical research might have been sacrificed at the expense of the increasing cost of funding clinical studies (it should be noted that in absolute terms there was a large increase in applied expenditures as well throughout this period). It is not known from these surveys how much of the relative scaling back in preclinical research affected discovery research compared with efforts in other areas.

Personnel are another surrogate of R&D investment. One advantage of the NSF survey is that it separates scientists and engineers from

other types of R&D personnel, which allows an examination of R&D investment in those personnel who are primarily responsible for performing the experiments and developing the processes that lead to drug innovations. This addresses the concerns expressed by some industry critics that R&D expenses reflect costs such as administration and market research that, they assert, are not relevant to pharmaceutical innovation. As shown in FIG. 4, the pattern of employment of scientists and engineers in the pharmaceutical industry largely parallels R&D expenditures as a percentage of net sales (compare with FIG. 2b). Furthermore, the ratio of pharmaceutical industry employment of scientists and engineers exceeds aggregate industry employment of such personnel by about the same ratio as pharmaceutical industry R&D spending exceeds aggregate industry R&D spending (that is, by two or three to one). More recent pharmaceutical industry

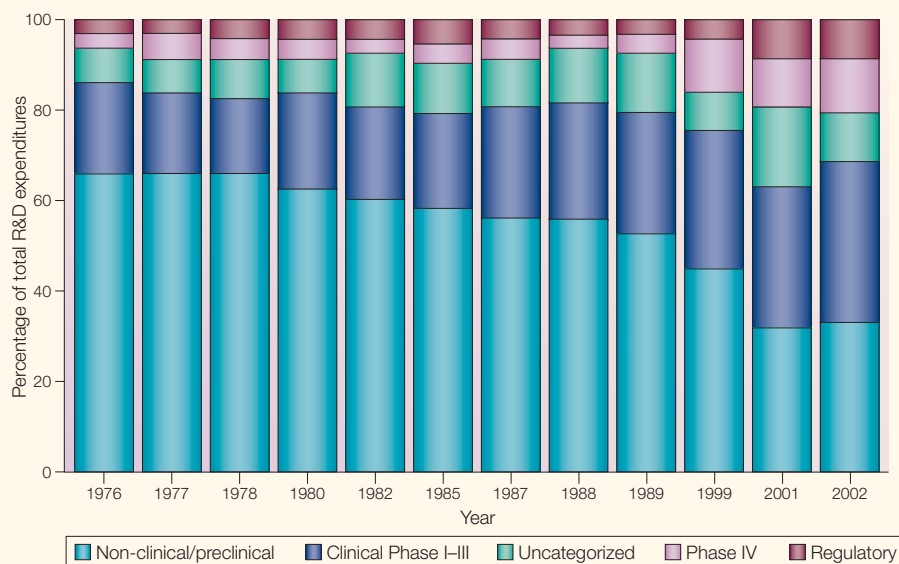


Figure 3 | Pharmaceutical industry allocation of R&D expenditures selected years 1976–2002. PhRMA used different categories than the NSF survey, and the PhRMA categories were changed after 1999. For this analysis, the earlier-years survey categories were collapsed to five to correspond with the more recent categorization. Allocation of funds summed to 100% for all years for which there were data. Stacked columns represent annual R&D expenditures as a percentage of total R&D allocated to: light blue, non-/preclinical research; blue, clinical Phases I–III; green, uncategorized R&D; pink, Phase IV clinical; and red, regulatory functions. Source: REFS. 13,26.

employment statistics indicate a trend of a steadily increasing proportion of scientists, relative to all pharmaceutical industry employees, for the past 5 years²¹ (data not shown).

Innovation output

Past and present drug approval trends. Between 1990 and 2003, the **Center for Drug Evaluation and Research** (CDER) of the US FDA approved 1,171 New Drug Applications (NDAs). Of these, 400 (34%) were New Molecular Entities (NMEs, defined as an

active ingredient that has never previously been marketed in the United States) and 771 (66%) were non-NMEs. Most commonly, ‘non-NME’ refers to new formulations of previously approved active ingredients. Of the NMEs approved, 166 (41% of NMEs) were granted priority-review status, compared with 98 (12.7%) priority-status non-NMEs. (A drug is assigned priority status when the drug product, if approved, would be a significant improvement compared with marketed products in the treatment, diagnosis or prevention

of a disease. The CBER definition of a priority review is stricter than the definition that CDER uses. The biological drug, if approved, must be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease). The trend of NDA approvals over time by therapeutic potential rating is shown in FIG. 5. With the exceptions of 1996 and 1997, which were particularly productive years for standard-rated NDA approvals, NDA approvals were generally stable throughout this interval. This is another way of saying that NDA approvals were not growing commensurately with the increase in R&D spending that occurred throughout this period (FIG. 2a).

In contrast to NDA approvals by CDER, the majority of which were for small-molecule drugs and diagnostics, Biologic License Application (BLA) approvals for recombinant protein drugs by the **Center for Biologics Evaluation and Research** (CBER) increased during this interval (from 11 between 1989 and 1996 to 17 between 1997 and 2002). The majority of BLA approvals for therapeutic proteins were granted to ‘biotech’ firms (17 out of 28) as opposed to traditional pharmaceutical firms (11 out of 28), but there was no trend suggesting a change in the innovators of such drugs with time²².

The priority-review classification provides a sense of the FDA’s judgment of the value of a new drug or use as it relates to previously approved drugs at the time of NDA filing. It is an unaudited, subjective determination that is subject to changes in personnel and policy, is limited to information available at the time of filing, and lacks strict guidelines for its application to individual drugs (but is otherwise a useful research tool). With that caveat in mind, FIG. 6a presents trends in NME filings (not approvals) with CDER for the interval 1995–2003. Two trends are worth noting. The first is that there has been a pronounced decline in recent NME filings with CDER, from 50 in 1995 to 24 in 2003. The second trend is that the ratio of priority- to standard-rated filings has increased year over year for 6 of the 8 years in this series. In 2003 there were as many priority-rated filings as standard-rated. This might be a coincidence, or it might reflect policy changes at CDER, but perhaps it helps explain why there are fewer NME filings in general. It seems reasonable to assume that priority-rated filings are preceded by higher-risk development programs than standard-rated filings. This is another way of implicating the theory of ‘low-hanging fruit’ in the decline of pharmaceutical productivity, which suggests that the easily picked fruit has already been harvested.

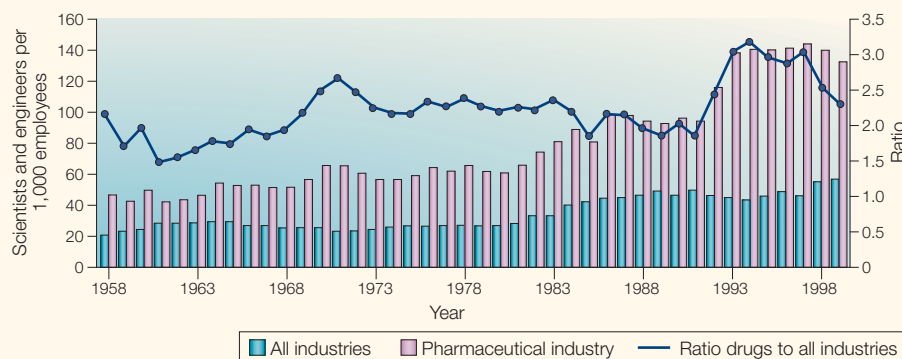


Figure 4 | Pharmaceutical industry scientific and engineering personnel compared with aggregate industrial scientific and engineering personnel 1958–1999. Light blue columns represent annual science and engineering employment expressed as number of active full-time equivalents (FTEs) per 1,000 FTEs employed for the aggregate of all industries represented in the National Science Foundation Annual Survey of Industrial Research and Development²⁰. Blue columns are data from the same surveys from just the pharmaceutical manufacturers (US Standard Industrial Classification 283). The blue curve represents the ratio of annual pharmaceutical science and engineering employment to aggregate industrial science and engineering employment.

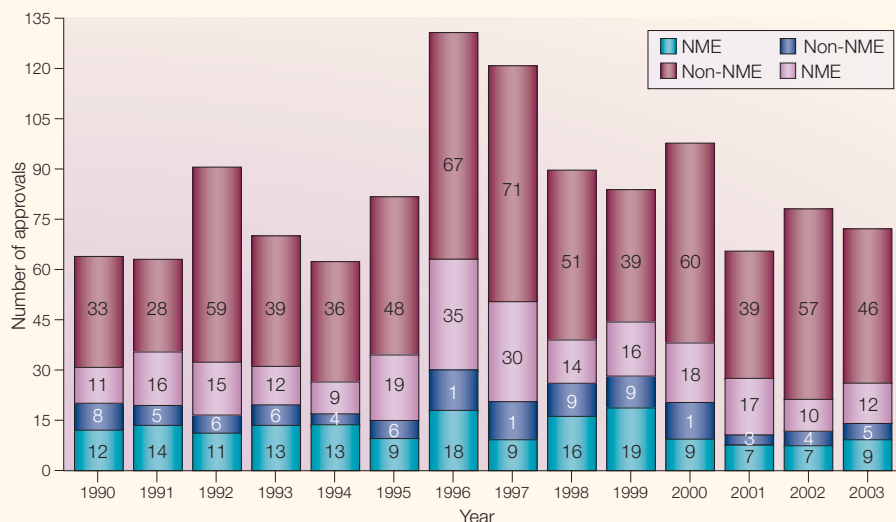


Figure 5 | **Center for Drug Evaluation and Research NDA approvals 1990–2003.** The light blue and blue stacked columns represent the number of priority-rated non-New Molecular Entity (NME) and NME New Drug Applications (NDAs), respectively, approved during the calendar year. The pink and red stacked columns represent approved standard-rated non-NME and NME NDAs, respectively. Source: Center for Drug Evaluation and Research.

As a means to assess its review performance according to the newly implemented user-fee goals of 1992, the FDA, beginning in fiscal year (FY) 1993, started tracking filings and actions taken on supplements to original NDAs (that is, efficacy supplements) separately from other NDAs. Efficacy supplements are filed when a new or modified indication or label change with new efficacy data is sought by the original manufacturer for previously approved drugs. Comparative efficacy claims, new dosage or route of administration, altered patient population, change in status from prescription to over-the-counter, and traditional approval following accelerated approval also require efficacy supplements. Efficacy supplement filings to CDER by fiscal year are shown in FIG. 6b. In contrast to NME filings, which declined in the past decade, efficacy supplement filings increased markedly, reaching a peak of 175 during FY 2000, a 90% increase over FY 1993 filings. More recently, efficacy filings have moderated slightly, but still remain 42% higher than in 1993. As discussed earlier, PhRMA members have indicated that R&D spending as a percentage of sales on sequential innovations — those that culminate in efficacy supplements — has remained stable over time. Therefore, either the pharmaceutical industry has developed processes that provide for relatively better productivity for sequential innovations as compared with non-sequential innovations, or opposing factors that influence one type of innovation preferentially, such as regulatory constraints, have eased with time.

At the same time as NME filings were increasing, the proportion of efficacy supplement filings granted priority-review designation was also increasing. Whereas just 7% of efficacy supplement filings were designated as priority in 1997, 19% were designated as such in 2002 and 2003. Because data for only 7 years are available, it is premature to reach definitive conclusions regarding a trend in

filing status. Nevertheless, the available data do not indicate a trend towards reduced quality of supplement filings. Therefore there is no evidence to support the criticism that the industry in general has focused its recent development efforts on minor modifications to existing drugs that have little social utility; indeed, the available data suggest the opposite.

The future? Having a glimpse of what is ‘on the horizon’ is perhaps the only advantage to a protracted product-development cycle. FIGURE 7 provides a look at trends in the aggregate active drug development pipeline, as determined by a sampling of a proprietary investigational drugs database at approximately the same time each year since 1995²³. There has been a marked trend towards increases in preclinical, Phase I and Phase II projects without a concomitant increase in Phase III projects. This is the Phase II roadblock that industry veterans speak of, the reasons for which remain unknown.

But all is not grim on the output front. As of May 2004, 56 drugs (all categories) had been approved, and another 165 were awaiting approval at the FDA. Nearly 400 Phase III programmes were ongoing — approximately equal numbers of which were for NMEs as for non-NMEs²⁴. Assuming an 80% probability that a given drug awaiting FDA approval will be launched, and a 60% probability of launch for the Phase III drugs in development, a total

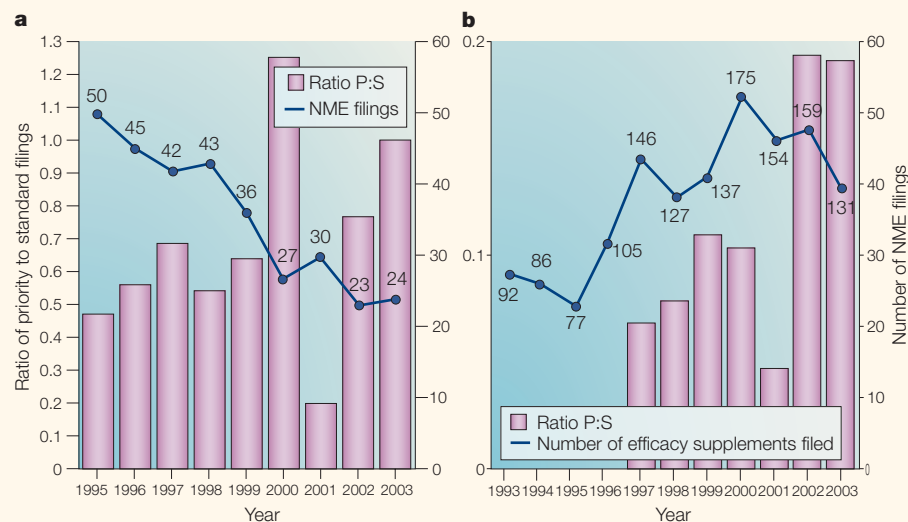


Figure 6 | **Recent trends in marketing authorization filings with the FDA.** **a** | New Molecular Entity (NME) filings with the Center for Drug Evaluation and Research (CDER) 1995–2003. The columns represent the ratio of priority- to standard-rated NME filings (P:S) received during each calendar year. The blue line and corresponding data label represent the total number of NME filings received by CDER during each calendar year. Source: REF. 29. **b** | Efficacy supplement filings with CDER 1993–2003. The columns represent the ratio of priority- to standard-rated efficacy supplement filings received during each fiscal year beginning with 1997 (the first year such data were summarized by the FDA). The blue line and corresponding data label represent the total number of efficacy supplement filings received by CDER during each fiscal year. Source: CDER.

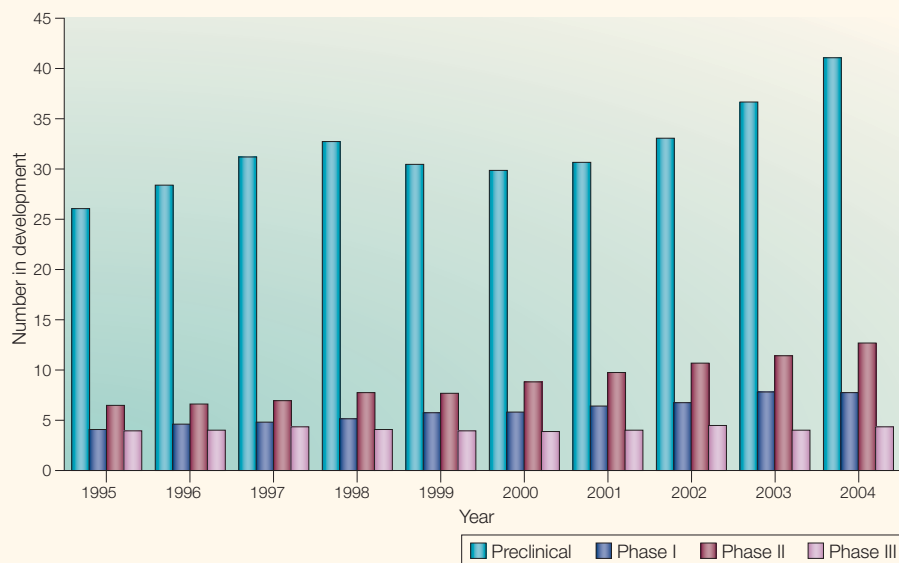


Figure 7 | **Drugs in development by Phase, 1995–2004.** Light blue, blue, red and pink columns represent preclinical, Phase I, Phase II and Phase III drugs, respectively, reported to be in active development during the first quarter of each year shown. Source: REF. 23.

of approximately 370 new drugs could be approved by the FDA within the next 3 or 4 years. This could represent as much as a 70% increase in innovative output compared with the 2001–2003 period.

Conclusions

The pharmaceutical industry is motivated to innovate, not just incrementally or sequentially but also to produce pioneering innovations that drive profits and provide competitive advantages. In this respect, it resembles most other mature manufacturing industries. Incremental innovations, for the most part, have an important role in sustaining the industry's incentives to innovate and should not be discouraged by policy. The evidence from R&D expenditures, allocation of R&D resources and drugs being produced, when taken together, support the industry's ongoing commitment to innovate. R&D investments as a percentage of sales are historically high relative to all other industries and are second only to the aerospace industry. As a proportion of funds invested in R&D, basic and applied research by industry is waning, and R&D investment is being apportioned increasingly to clinical development and regulatory requirements. It is not clear whether this nonclinical research gap is being filled by non-profit institutional research, but the increased issuance of drug patents to universities and colleges suggests that this is indeed occurring. Fewer NMEs are being approved, including fewer priority-rated NMEs. But on the basis of NME filings, the decline in priority-rated

NME approvals does not seem to be related to an industry aversion to developing drugs destined for a priority review, because the proportion of NME and efficacy supplement filings that receive this rating has been increasing, not decreasing, recently. Finally, the future looks brighter in terms of innovative output, with the possibility for large relative increases in new drug approvals over the coming few years.

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Competing interests statement

The author declares no competing financial interests.

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