Lessons from 60 years of pharmaceutical innovation

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Abstract | Despite unprecedented investment in pharmaceutical research and development (R&D), the number of new drugs approved by the US Food and Drug Administration (FDA) remains low. To help understand this conundrum, this article investigates the record of pharmaceutical innovation by analysing data on the companies that introduced the ~1,200 new drugs that have been approved by the FDA since 1950. This analysis shows that the new-drug output from pharmaceutical companies in this period has essentially been constant, and remains so despite the attempts to increase it. This suggests that, contrary to common perception, the new-drug output is not depressed, but may simply reflect the limitations of the current R&D model. The implications of these findings and options to achieve sustainability for the pharmaceutical industry are discussed.

New molecular entity
(NME). A medication containing an active ingredient that has not been previously approved for marketing in any form in the United States. NME is conventionally used to refer only to small-molecule drugs, but in this article the term includes biologics as a shorthand for both types of new drug.

Prescription Drug User Fee Act
A US law passed in 1992 that allows the US Food and Drug Administration to collect fees from drug manufacturers to fund the new-drug approval process.

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From 1950 to 2008, the US Food and Drug Administration (FDA) approved 1,222 new drugs (new molecular entities (NMEs) or new biologics). However, although the level of investment in pharmaceutical research and development (R&D) has increased dramatically during this period — to US$50 billion per year at present[1] — the number of new drugs that are approved annually is no greater now than it was 50 years ago. Indeed, in 2008, only 21 new drugs were approved for marketing in the United States, which is well below the level required to secure the future of the pharmaceutical industry.

With the aim of investigating this issue, this article analyses the output of new drugs — NMEs or new biologics approved by the FDA — from the companies responsible during the past 60 years (see BOX 1 for details of the methodology). This analysis shows that the rate of production of new drugs by these companies has been constant (although the rates differ for each company) since they began producing drugs. Surprisingly, nothing that companies have done in the past 60 years has affected their rates of new-drug production: whether large or small, focused on small molecules or biologics, operating in the twenty-first century or in the 1950s, companies have produced NMEs at steady rates, usually well below one per year. This characteristic raises questions about the sustainability of the industry's R&D model, as costs per NME have soared into billions of dollars. It also challenges the rationale for major mergers and acquisitions (M&A), as none has had a detectable effect on new-drug output. Finally, it suggests that drug companies need to be bolder in redesigning their research organizations if they are to escape the increasing pressures created by linear new-drug output and rapidly rising R&D costs.

Rate of new drug introduction

Of the 1,222 NMEs that have been approved since 1950, 1,103 are small molecules and 119 are biologics. FIGURE 1a shows the timeline of these approvals. Although at first glance there are no obvious patterns, on closer observation subtle trends emerge. For the 30 years between 1950 and 1980, the trend line is basically flat. Then for the next 15 years, the curve slopes gently upwards, culminating in 51 approvals in 1996, 4 years after the enactment of the Prescription Drug User Fee Act (PDUFA). Since 1996, approvals have returned to their historical range. There has been speculation that the peak in 1996 was caused by the FDA processing a backlog of applications with the help of the recently approved user fees. Although this may have played a part, other factors were involved, as discussed below. A second trend is that approvals of biologics are not taking off as might be expected from a new technology.

Many players, but few winners

At present, there are more than 4,300 companies that are engaged in drug innovation[2], yet only 261 organizations (6%) have registered at least one NME since 1950. Of these, only 32 (12%) have been in existence for the entire 59-year period. The remaining 229 (88%) organizations have failed, merged, been acquired, or were created by such M&A deals, resulting in substantial turnover in the

Box 1 | **Data collection and analysis**

Definitions

- For the purpose of this study, an innovation is a new molecular entity (NME) or a new biologic approved by the US Food and Drug Administration (FDA), and excludes non-drug compounds such as imaging agents and cosmetics. This article uses NME as shorthand for both types of drugs.
- Biologics are all therapeutic proteins, regardless of their approval route.
- A blockbuster is defined here as an NME the peak sales of which exceed $1 billion, expressed in year-2000 dollars equivalent. Figures have been adjusted for inflation using the US Bureau of Labor Statistics' Drug Inflation Index.
- A large pharmaceutical company is one of the top 15 drug companies, or their predecessors and joint ventures (for example, Ciba, SmithKline and DuPont–Merck). All other companies, including biotechnology companies, are categorized as small pharmaceutical companies.

Data sources

- NME data were obtained from the FDA under a freedom-of-information request, and were cross-checked against Lilly's own record, as well as lists of FDA approvals that are routinely published in the press. When several companies have collaborated on the development of a drug, or the ownership of the compound has changed before approval, the company receiving FDA approval has been credited with the innovation.
- Sales and patent data were obtained from the EvaluatePharma Database (see Further information).
- Inflation data were obtained from the US Bureau of Labor Statistics.

Tools

- All statistical calculations were done with the JMP software, version 5.1.1, or Excel 2007.

Exclusions

- 11 organizations out of 261 (accounting for 13 NMEs out of 1,222) are non-commercial entities (non-profit and governmental organizations) or companies that no longer exist and have been omitted from most of the analysis. Of the remaining 250 companies, 26 (accounting for 63 NMEs) had fewer than 10 data points and were also excluded from most of the analysis.

Potential limitations

- It could be argued that defining innovation as NMEs approved by the FDA does not give due credit to innovation originating outside the United States. However, because the pharmaceutical industry is global, and the United States is by far its largest market, most NMEs are eventually submitted to the FDA for approval.
- There is some debate about the number of NMEs that were approved prior to the US Kefauver–Harris amendment of 1962, which requires proof of effectiveness and safety before a drug can be registered. Data that were compiled at the time by de Haen and used in a congressional testimony by FDA Commissioner Alexander Schmidt in 1974 show that 360 NMEs were approved between 1951 and 1962, or ~30 per year. It seems that this figure was subsequently revised by the FDA, and reduced to 227. As this occurred a long time ago, it is difficult to reconstruct what happened. However, the editing seems to have been careful, as the data provided by the FDA meticulously listed each drug by its brand name and active ingredient, as well as its dosage form, sponsor and exact date of approval. The 133 missing potential NMEs were evidently excluded for a reason and, lacking evidence to challenge it, the data were used as provided.
- It might be argued that NMEs are an inappropriate measure of innovation because a molecule with little therapeutic value can conceivably be approved, provided it meets FDA requirements. However, given the costs of drug research and development, this is unlikely to occur in practice. A drug that is innovative may nevertheless fail to generate substantial sales revenues, raising questions about the value of its innovation (for example, as with Pfizer's inhaled insulin product Exubera). This article considers that these molecules represent genuine advances and should count as innovation, as their market failure can be explained by several factors that are unrelated to innovation, such as mispricing, reluctance on the part of physicians or patients to change from established drugs, and competition.
- The decision to credit the company that secures a drug approval with the corresponding innovation could be questioned, because that molecule may have been licensed from another company that receives no credit. As licensees are often thought to be large companies, and licensors smaller ones, this could potentially bias the analysis by giving certain companies more, or less, credit than warranted. However, this concern does not seem to be justified. Over the past 20 years, a thriving market for innovation has developed, involving thousands of collaborations each year — including licensing, cross-licensing, sublicensing, joint discovery, co-development, buy-back options, loans, equity stakes, outsourcing, warrants and joint ventures — which often makes it impossible to assess the precise contribution made by a company to the approval of a new drug. In addition, small companies are eager participants in this market, in which they collaborate with other small companies more frequently than with large ones. Between 1980 and 2004, small companies had a slightly greater share of discovery projects than did larger companies (47% versus 38%), but both shared equally in the number of development projects (45% versus 46%)[42]. The view that the division of labour might allow large companies to capture a greater share of development projects and FDA approvals is therefore not supported by the data. In addition, as innovation networks spread, the locus of innovation tends to shift from individual companies to the network[43]. So, the decision to credit the company at the centre of that network with the innovation that it creates seems to be justified, especially given that, by organizing and managing the network to gain FDA approval, that company often makes the greatest contribution to the process.

industry (FIG. 1b). Of the 261 organizations, only 105 exist today, whereas 137 have disappeared through M&A and 19 were liquidated.

Despite this intense turnover, the fact that 32 companies have survived the entire period suggests that there are ways to innovate that are sustainable. This group includes 23 companies that have found unique ways to thrive despite their smaller size. Some are highly focused on a particular disease area or therapeutic strategy (Novo Nordisk, Ferring, Grifols, UCB, Endo and Purdue); some sell products and services in addition to drugs (Bausch and Lomb, and Allergan); some are entrenched in their home-country market (Takeda, Santen, Eisai, Angelini and Orion); some are conglomerates (Boehringer–Ingelheim, Solvay, Baxter and Carter–Wallace); and some concentrate on generics (Teva and Mission Pharmacal).

At the high end of the innovation scale, 21 companies have produced half of all the NMEs that have been approved since 1950, but half of these companies no longer exist. FIGURE 1c shows that Merck has been the most productive firm, with 56 approvals, closely followed by Lilly and Roche, with 51 and 50 approvals, respectively. Given that many large pharmaceutical companies estimate they need to produce an average of 2–3 NMEs per year to meet their growth objectives, the fact that none of them has ever approached this level of output is concerning.

The dynamics of drug innovation

The timelines of cumulative NME approvals for the three most productive companies in the industry are shown in FIG. 2a. Surprisingly, the plots are almost straight lines, indicating that these companies have delivered innovation at a constant rate for almost 60 years. The outputs from less productive companies, some of which are plotted in FIG. 2b, show a similar linear pattern, although it is more erratic and with smaller slopes. The stable rates of output that are apparent in FIGS 2a,b suggest that NME production at a pharmaceutical company follows a Poisson distribution. This hypothesis is confirmed by the statistical analysis described in Supplementary information S1 (box)).

Importantly, as Poisson distributions are characterized by a constant but stochastically variable rate of occurrence, this implies that the average annual NME output of drug companies is constant, and has been so for nearly 60 years. This is consistent with the fact that the drug industry produces no more NMEs today than 60 years ago, which has important implications. If nothing that drug companies have done in the past 60 years has succeeded in raising their mean annual NME output, there is not a high probability that established strategies will change this now. FIGURE 2c shows that the industry's NME output has tracked its expected values. This suggests that the output may not be depressed, as commonly thought, but may simply reflect the innovative capacity of the established R&D model. As the integrated corporate laboratory is one of the few features shared by companies during the 60-year period, it is possible that the constant NME output is a fixture of that model. If this is true, the industry's efforts to embrace new approaches to innovation, such as open innovation[3], are of particular importance.

Another surprising finding is that companies that do essentially the same thing can have rates of NME output that differ widely. This suggests there are substantial differences in the ability of different companies to foster innovation. In this respect, the fact that the companies that have relied heavily on M&A (FIG. 2b) tend to lag behind those that have not (FIG. 2a) suggests that M&A are not an effective way to promote an innovation culture or remedy a deficit of innovation.

If the NME output of drug companies is constant, the only way to increase the overall industry output is to increase the number of companies, which runs counter to the surge of M&A activity of the past 12 years. Indeed, FIG. 2c suggests that there may be a correlation between the expected NME output for the industry (on the basis of the analysis described in Supplementary information S1 (box)) and the number of companies involved. A closer examination of this relationship (FIG. 2d) confirms that the expected NME output and the number of companies are closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output by changes in the number of companies. As the number of companies increases, the expected NME output increases more than proportionally. One possible interpretation is that a larger number of companies accelerates the acquisition of knowledge, creating what economists call a spillover — an industry-wide benefit that enables all companies to be more productive. This has important implications for the design of new R&D models.

As can be seen in FIG. 2c, actual NME output for 1996–1997 clearly lies outside the 95% confidence band of its expected value, suggesting that an external factor temporarily boosted the number of NMEs that were approved. Several explanations have been offered, most of which centre on the impact of the PDUFA of 1992. They include a clearing of the backlog of new drug applications that were submitted before 1992; the setting of performance goals that required swift action on post-1992 submissions; a surge of post-1992 submissions to take advantage of PDUFA before it might expire; and a temporary acceleration of drug R&D across the industry to try to increase NME output. These hypotheses are not amenable to statistical testing, but the last two can be readily dismissed, as they are not consistent with the way the industry works. The factor relating to performance goals may have played a part, but much of the surge can probably be ascribed to the clearing of the backlog of new drug applications.

As the output of new biologics also follows a Poisson distribution, its pattern is similar to that for NMEs, in which approvals fluctuate around a constant, low level (FIG. 1a). This has led to the suggestion that biotechnology is not delivering on its promise to increase the rate of innovation because it has co-opted the pharmaceutical industry's ageing business model instead of crafting its own[4].

Lastly, further statistical analysis (see Supplementary information S2 (box)) can be used to calculate the probability that a company's NME output will exceed 2 or

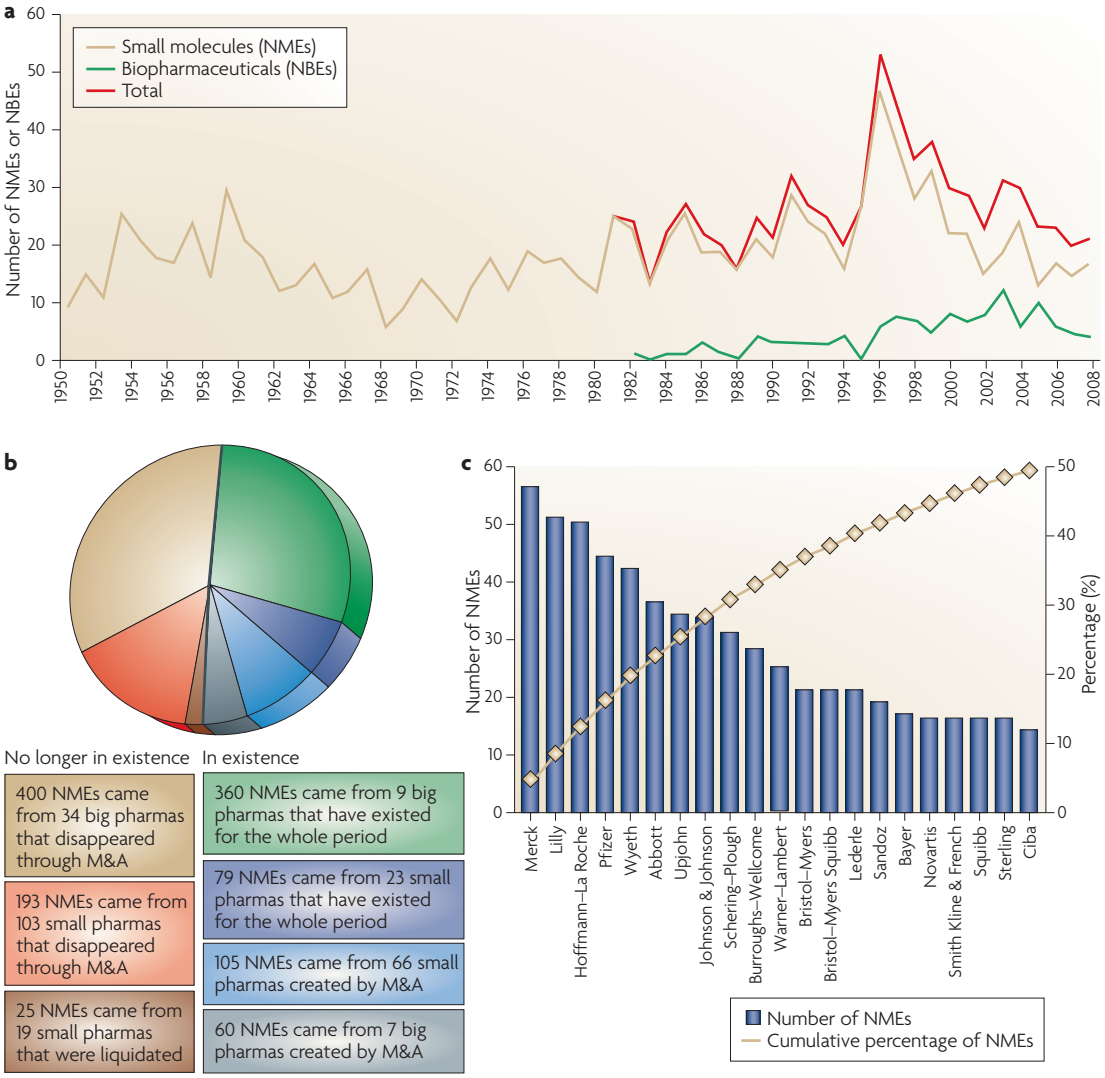


Figure 1 | **Origins of new drugs. a** | Timeline of approvals of new molecular entities (NMEs) and new biological entities (NBEs) by the US Food and Drug Administration (FDA) between 1950 and 2008. **b** | Characteristics of the 261 organizations that have produced the 1,222 NMEs approved since 1950. **c** | 21 companies have produced half of all the NMEs that have been approved since 1950, although half of these companies no longer exist . In parts **b** and **c**, both new small molecules and new biologics are grouped as NMEs for simplicity. M&A, mergers and acquisitions. For details of the analysis, see BOX 1.

3 per year, which are 0.06% and 0.003%, respectively. It is therefore unlikely that most companies will succeed in raising their NME output above what they consider to be their threshold of sustainability. It is equally unlikely that the industry will achieve an overall output that is much greater than the current one.

The cost of NMEs

The cost per NME has been increasing for decades. FIGURE 3a displays 12 independent NME cost estimates[5–14] spanning 48 years, and FIG. 3b plots the same data on a logarithmic scale. Both charts show that NME costs have been growing exponentially at an annual rate of 13.4% since the 1950s.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the members of which are mostly large drug companies, R&D spending has been growing at an average compounded rate of 12.3% since 1970 (REF. 1). Although the overall output of NMEs has therefore stagnated, the industry is producing them more efficiently as it has been able to meet the increase in the cost per NME with a less than commensurate increase in R&D spending. In other words, the industry is better at what it does than it was previously, much of which is to generate data to meet FDA requirements. However, this increased efficiency has not translated into a sustained increase in the discovery of new treatments.

DiMasi has estimated that the average cost per NME was $802 million in 2000 for small molecules[8], and $1,318 million in 2005 for biologics[11]. These averages, however, do not include post-approval costs for Phase IV

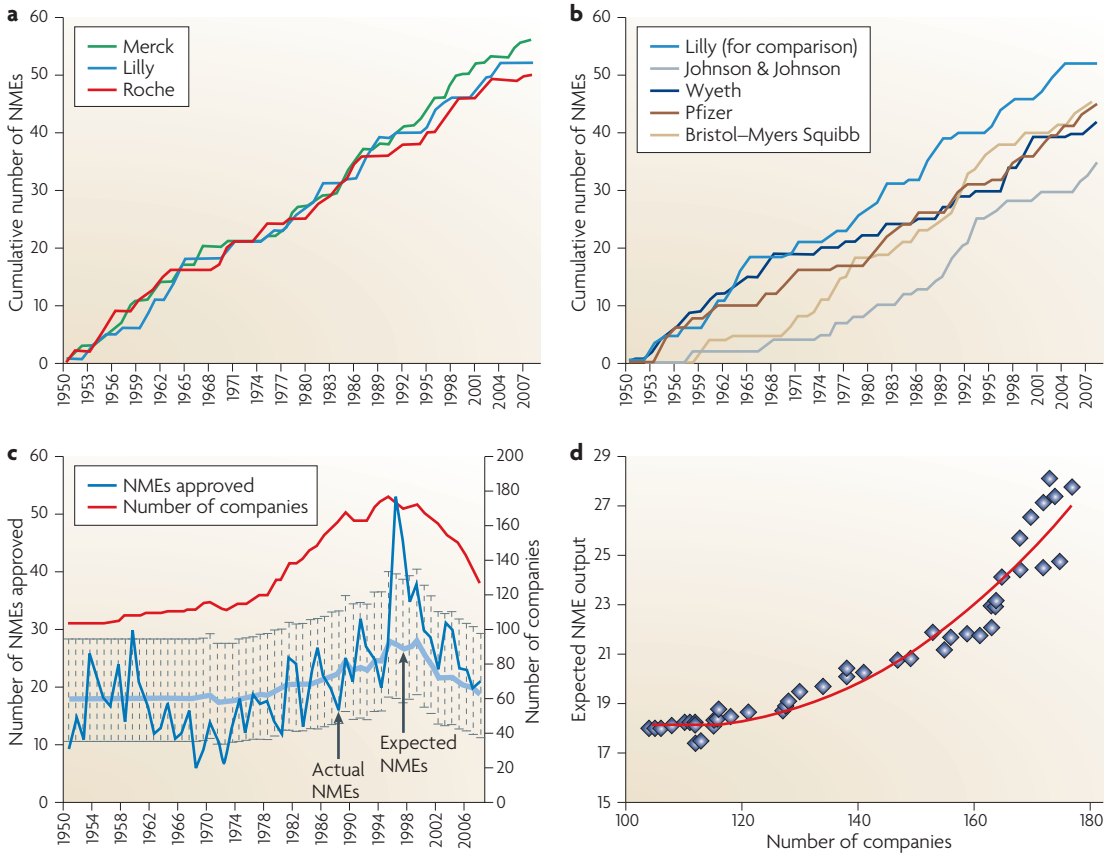


Figure 2 | **The dynamics of drug innovation. a** | The cumulative number of new molecular entities (NMEs) originating from the three most productive companies over the period studied: Merck, Lilly and Roche. **b** | The cumulative number of NMEs from selected companies that have been heavily involved in mergers and acquisitions, with Lilly included for comparison. **c** | The NME output of the industry closely tracks the expected value on the basis of the analysis described in Supplementary information S1 (box), suggesting that output is not depressed at present, but simply reflects the innovative capacity of the established research and development model. **d** | The expected NME output and the number of companies are closely correlated in a nonlinear relationship that explains 95% of the changes in expected NME output by changes in the number of companies.

studies that might be required by the FDA; they also omit costs to gain regulatory approval in non-US markets or obtain additional label claims for new indications. Most importantly, they assume that the probability that a molecule will successfully emerge from clinical trials is about 21.5%, whereas recent industry data suggest that this value is 11.5%. When DiMasi's figures are adjusted for these items as well as for inflation and other cost increases (for example, owing to more stringent regulatory requirements), the cost per NME increases considerably, as summarized in FIG. 3c. These averages also conceal potentially large differences between companies. For example, between 2000 and 2008, Pfizer spent a total of $60 billion on R&D, and received FDA approval for nine NMEs. By contrast, Progenics, which received FDA approval for methylnaltrexone bromide (Relistor) in 2008, spent $400 million on R&D over the same period, suggesting a cost per NME that is substantially lower than Pfizer's.

Estimating the cost of NMEs is complex because the money spent on R&D is returned in revenue over several years. R&D expenses should therefore be depreciated over that period. However, the duration of this period is unclear, and has probably changed over time, as science and regulations have transformed drug research. Practically, there is little consensus among experts on how to capitalize and depreciate drug R&D. Published studies have used periods ranging from 4 to 12 years.

However, the finding that drug companies produce NMEs at a constant rate makes it possible to develop simple estimates of NME costs at a company level by dividing each company's annual R&D spending by its rate of NME production. FIGURE 3d shows the distribution of NME costs across the industry for 2008. Only 27% of companies have costs per NME below $1.0 billion. The magnitude of these figures is worrying and calls for more research to fully understand the implications.

Does regulation hinder innovation?

The growth in R&D spending is needed to offset inflation and the increasing burden of regulation, as well as other factors that could be contributing to greater costs, such as higher failure rates. As inflation has been ~3.7% since 1950 and the annual growth in R&D spending has

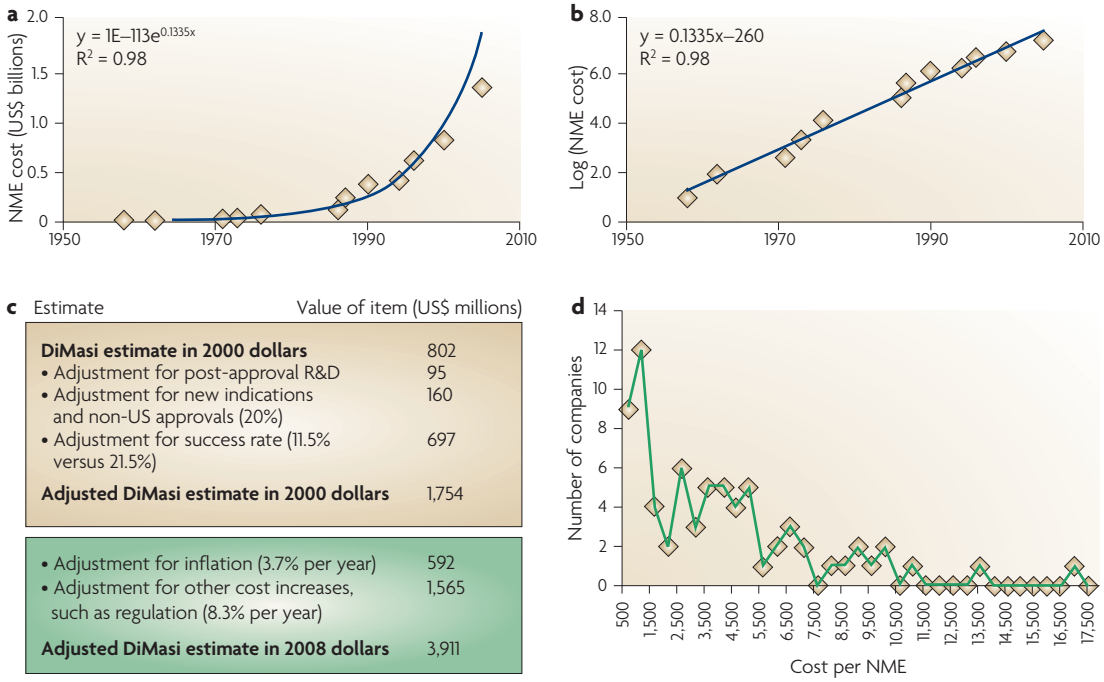


Figure 3 | **The cost of new drugs. a** | A plot of twelve independent estimates of the cost of a new molecular entity (NME) spanning 48 years[5–14]. **b** | The same data plotted on a logarithmic scale. The exponent in the line equation in part **a** and the gradient of the line in part **b** show that the cost per NME has grown at an annual compound rate of 13.35% since the late 1950s. **c** | Adjusted costs per NME: 2000 versus 2008. **d** | Distribution of costs per NME for the industry in 2008.

been 12.3%, one can infer that regulatory and other costs have been growing at ~8.3% annually, which translates into a doubling every 8.5 years. This increase has often been attributed to the increasing prudence of regulatory bodies following the high-profile withdrawals of drugs such as rofecoxib (Vioxx; Merck), cerivastatin (Baycol; Bayer), troglitazone (Rezulin; Warner-Lambert) and cisapride (Propulsid; Janssen Pharmaceutica).

The evidence available on the effect of regulation on innovation is more nuanced. It is interesting that a 1983 study of the drug industry by the National Academy of Engineering[15] had already noted the increasing regulatory burden, and voiced concern that the resulting higher cost of innovation in the United States was undermining the competitiveness of the US drug industry and putting it at a disadvantage compared with its European and Japanese competitors. In fact, the opposite happened: since that report was published, US pharmaceutical companies have outperformed their international competitors and emerged as the dominant force in the industry.

A possible reason for this paradox can be found in other research published at about the same time[16]. It shows that countries with a more demanding regulatory apparatus, such as the United States and the UK, have fostered a more innovative and competitive pharmaceutical industry. This is because exacting regulatory requirements force companies to be more selective in the compounds that they aim to bring to market. Conversely, countries with more permissive systems tend to produce drugs that may be successful in their home market, but are generally not sufficiently innovative to gain widespread approval and market acceptance elsewhere. This is consistent with studies indicating that, by making research more risky, stringent regulatory requirements actually stimulate R&D investment and promote the emergence of an industry that is research intensive, innovative, dominated by few companies and profitable[17,18].

Is bigger better?

A puzzling trend of recent years has been the gradual erosion in the share of innovation that is captured by NMEs sponsored by large pharmaceutical companies (see BOX 1 for definitions). Since the early 1980s, their share of NMEs has declined from ~75%, a level that had been constant since 1950, to ~35% (FIG. 4a). At the same time, the share of NMEs that is attributable to small biotechnology and pharmaceutical companies has almost trebled, from ~23% to nearly 70%. Since 2004, small companies have consistently matched or outperformed their larger competitors. The expected share of NMEs generally follows these trends until 2004, when they stabilize at about 50% each.

The increase in the NME output from small companies has been driven by two factors. The first is a rise in the number of small companies that have produced an NME, which nearly doubled from 78 to 145 during the 1980s and 1990s. This was facilitated by the growth of venture capital that has funded much of the 'biotech boom'. Second, the mean annual NME output of small companies

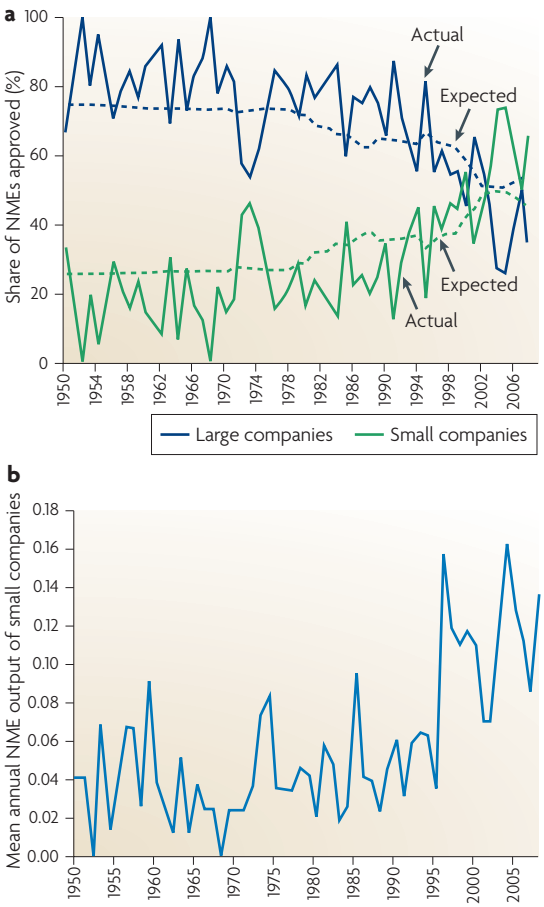


Figure 4 | **Is bigger better? a** | Actual versus expected shares of new molecular entities (NMEs) for large and small pharmaceutical companies. **b** | Mean annual NME output for small companies. See BOX 1 for definitions.

has increased from ~0.04 to ~0.12 since 1995, owing to the emergence of new, more productive companies (FIG. 4b). Conversely, the decline in the output of large companies has been driven by the dwindling number of large pharmaceutical companies, which has decreased by 50% over the past 20 years.

It is too early to tell whether the trends of the past 10 years are artefacts or evidence of a more fundamental transformation of the drug innovation dynamics that have prevailed since 1950. Hypotheses to explain these trends, which could be tested in the future, include: first, that the NME output of small companies has increased as they have become more enmeshed in innovation networks; second, that large companies are making more detailed investigations into fundamental science, which stretch research and regulatory timelines; and third, that the heightened safety concerns of regulators affect large and small companies differently, perhaps because a substantial number of small firms are developing orphan drugs and/or drugs that are likely to gain priority review from the FDA owing to unmet medical needs.

According to a recent report[2], the 4,300 biotechnology companies spend ~$28 billion annually on R&D, compared with $50 billion for large pharmaceutical companies[1]. By virtue of their number, small firms collectively can explore far more directions, and investigate areas that their larger, more conservative competitors avoid. However, only a small fraction of these small companies will be rewarded with an FDA approval. Individually, they are a much less reliable source of NMEs than large companies, but collectively, they produce more, for less. In this strange equation lies perhaps one potential avenue for renewing the pharmaceutical R&D model. The innovation crisis of the pharmaceutical industry is occurring in the midst of a new golden age of scientific discovery. If large companies could organize innovation networks to harness the scientific diversity of biotechnology companies and academic institutions, and combine it with their own development expertise, they might be able to reverse the forces that are undermining their research model; that is, they might be able to lower their costs and increase their output.

Is consolidation good for innovation?

M&A activity is often seen as a strategy to tackle a thinning pipeline. Using the data collected for this study, this strategy can be tested by measuring the 'before and after' Poisson parameters of companies that have engaged in these transactions (as the expected NME output of a group of companies is equal to the sum of their Poisson parameters). The population in this study has 24 acquisitions and 6 mergers with a minimum of 10 years of data before and after each transaction. FIGURE 5a summarizes the collective expected annual NME output of the companies involved. Only small companies show a slight, but significant, increase in NME output at the 95% confidence level. For large companies, M&A do not seem to create or destroy value. In fact, one can summarize the impact of M&A in the pharmaceutical industry on R&D as '1+1=1'. This is consistent with a recent analysis[19].

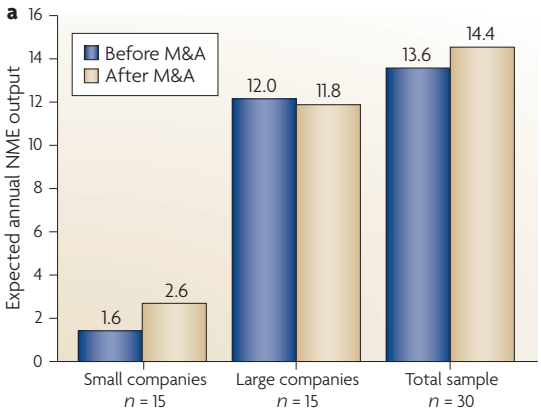
A more detailed analysis adds interesting nuances. FIGURE 5b looks separately at M&A involving large and small companies. For large companies, half of the six mergers analysed increased NME output (by 44%), whereas the other half reduced NME output (by 36%). For small companies, nearly 80% of acquisitions increased NME output (by 118%), whereas the rest reduced NME output (by 33%). For large companies, the proportions were reversed: 70% of acquisitions reduced NME output (by 20%), whereas 30% of acquisitions increased NME output (by 41%). Caution should be taken in interpreting these numbers because of the small sample size. In addition, many companies involved in M&A since 2000 were not included in the analysis because they did not meet the inclusion criteria of 20 years of data. This analysis will need to be repeated as more data become available. For now, the evidence suggests that M&A can help small companies, but are not an effective means to boost NME output among larger companies.

What next?

Scaling patent cliffs. Not only is the discovery of NMEs elusive, but their sales prospects are highly skewed towards zero, further reducing the likelihood of obtaining

Orphan drug
A drug that is specifically developed for a disease that affects a patient population of fewer than 200,000 people in the United States. The Orphan Drug Act provides financial incentives to develop such drugs, including marketing exclusivity for that indication for 7 years after approval.

a



b

	Mergers (large companies)	Acquisition involving Small companies	Large companies
Number of companies	6	14	10
Resulted in greater NME output	50%	79%	30%
NME increase (%)	44%	118%	41%
Resulted in lower NME output	50%	21%	70%
NME decrease (%)	–36%	–33%	–20%

Figure 5 | **Impact of industry consolidation. a** | Impact of mergers and acquisitions (M&A) on new molecular entity (NME) output. For small companies, there is a 95% probability that M&A has increased NME output slightly. However, for large companies, and for the total sample, there is a 95% probability that M&A did not increase NME output. **b** | Value created by M&A. See BOX 1 for definitions.

a return on investment in R&D. FIGURE 6a plots the frequency distribution of peak sales for NMEs. It is based on 329 of the more recent NMEs for which such data are available. The underlying data show that the probability that an NME will achieve blockbuster status is ~21%, a success rate that has not changed in 20 years despite considerable investment to improve the chances of success. This low probability is seen even though large pharmaceutical companies and venture capitalists will seldom proceed with the development of a molecule unless it has blockbuster potential, supported by sophisticated forecasts and reviews by experienced executives.

More worryingly, it also suggests that the industry's most hallowed competencies — customer knowledge, disease expertise and decades of experience — do not seem to be of much help in predicting success[20]. This forces the industry to navigate without a reliable road map, which is a challenge it shares with other blockbuster-dominated businesses such as motion pictures or oil and gas exploration. This has important implications for the management of innovation, which is discussed in the next section.

It is now possible to combine knowledge of drug innovation and new-product sales with patent expirations to model how drug companies might survive the large upcoming revenue losses caused by the expiration of patents on key blockbuster drugs, something often referred to as 'patent cliffs' (see Supplementary information S3 (box) for a description of this simulation tool). FIGURES 6b,c summarize the results for the 13 largest pharmaceutical companies, created by using this tool to generate probability distributions for sales and net income that reflect the stochastic nature of drug innovation at the company level. The results indicate that continuing with the current business model may result in a reduction of 5–10% in sales and 20–30% in net income in 2012–2015. Sales should subsequently recover to their 2011 peak, but net income may remain down by 15% — a performance that is unlikely to please stakeholders.

Choosing a course. If the performance of the current business model cannot satisfy stakeholders, M&A are not a solution, and the process improvements and cost-cutting measures that are commonly used cannot make a sufficient difference, perhaps the industry ought to embrace more radical change and seize the opportunity to redesign the model. Four points to consider in discussions on such a redesign can be put forward on the basis of the analysis in this article.

First, the industry needs to change its innovation dynamics to move beyond constant NME output. This is a daunting task. As nothing that the industry has done in the past 60 years has substantially affected mean output, it must venture further away from its comfort zone as it rebuilds its R&D model. As was noted by the previous Chief Executive Officer of GlaxoSmithKline, Jean-Pierre Garnier[21]: "R&D productivity is the number one issue". If it is not fixed, nothing else can work.

Second, there are radical and successful experiments that can be used as building blocks or for inspiration; for example, Innocentive[22,23], Chorus[24], public–private partnerships[25–27], open-source R&D[28–30], X Prize[31], innovation networks[32], FIPNet[33], consortia and various combinations of these and other initiatives[34]. These efforts aim to harness the 'global brain' to access the best science and ideas wherever they may be. Such open architecture for R&D has key advantages: it heightens competition, reduces costs and increases agility by making it easier to initiate and terminate projects. More importantly, it makes it easier to manage 'disruptive innovation' by locating it outside the corporate walls, where it can thrive unencumbered.

Third, in many organizations, short-term priorities encourage marginal innovation, which provides more reliable returns on investment, at the expense of major change. Therefore, organizations that depend on breakthrough discoveries need a separate, protected area the sole purpose of which is disruptive innovation. In the past, this was provided by independent laboratories, such as Bristol–Myers Squibb's Pharmaceutical Research Institute or Merck Research Labs. However, these units were never quite able to free themselves from corporate attempts to increase the number of blockbusters by making scientists more responsive to market needs. The result has usually been a greater emphasis on imitative research, fewer breakthroughs and drugs that miss the blockbuster mark 80% of the time.

Open-source R&D
A broad-based participatory research model in which a virtual network of volunteers use online tools to address a problem in which they share an interest.

Disruptive innovation
A process to turn cutting-edge science into novel products with such superior features that they create vast new markets, which unsettles established products and technology.

Black swan
A metaphor that designates rare random events of key importance that reshape markets, industries and societies.

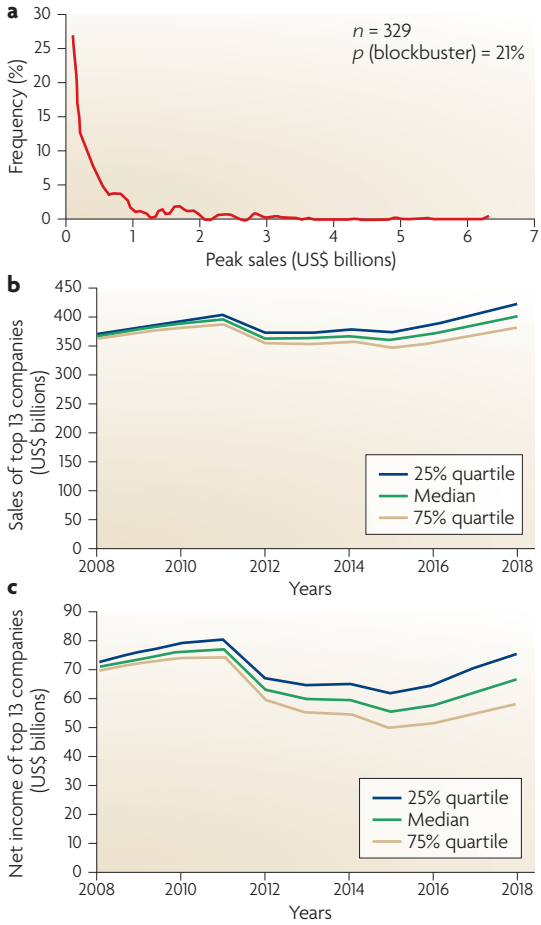


Figure 6 | **Sales of new molecular entities (NMEs).** **a** | Frequency distribution of peak sales for NMEs. **b** | Predicted sales for the top 13 pharmaceutical companies from 2009–2018. **c** | Predicted net income for the top 13 pharmaceutical companies from 2009–2018.

Fourth, the industry must rethink its process culture. Success in the pharmaceutical industry depends on the random occurrence of a few 'black swan'[35] products. Common processes that are standard practice in most companies create little value in an industry dominated by blockbusters[36]. These include developing sales forecasts for new products, which are inaccurate nearly 80% of the time. Another example is portfolio management, which has been widely adopted by the industry as a risk management tool, but has failed to protect it from patent cliffs. During the past couple of decades, there has been a methodical attempt to codify every facet of the drug business into sophisticated processes, in an effort to reduce the variances and increase the predictability. This has produced a false sense of control over all aspects of the pharmaceutical enterprise, including innovation. As Jean-Pierre Garnier puts it: "The leaders of major corporations including pharmaceuticals have incorrectly assumed that R&D was scalable, could be industrialized and could be driven by detailed metrics and automation. The grand result: a loss of personal accountability, transparency and the passion of scientists in discovery and development"[37].

Conclusion

In the past 60 years, the pharmaceutical industry has delivered over 1,220 new drugs that have played an important part in improving public health and extending life expectancy by an average of 2 months each year[38]. The R&D model that has powered that success, however, is showing signs of fatigue: costs are skyrocketing, breakthrough innovation is ebbing, competition is intense and sales growth is flattening. This cluster of symptoms has often foretold major disruption in other industries[39,40]. Their experiences show that industries can survive such upheavals; someone always finds a way to redesign the business model, but that someone, ominously, has seldom been an incumbent[41].

Could pharmaceuticals be different? Drug research today is the locus of many interesting experiments that have the potential to rejuvenate the R&D model. Many of them are taking place in areas that have traditionally been overlooked by the large companies, such as neglected diseases and biodefence, which is consistent with the predictions of Clayton Christensen[41]. Nevertheless, large companies have also sponsored some highly innovative concepts, some of which are highlighted in the previous section. However, although these experiments are proceeding, the industry is increasingly caught in a pincer between an NME output that is essentially linear, and likely to remain so, and a cost of producing NMEs that is increasing exponentially. At some point, the situation will become untenable. This could tempt investors to force wholesale change onto the industry, unless the industry pre-empts them with radical initiatives.

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Competing interests statement
The author declares competing financial interests: see web version for details.

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