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Why the drug development pipeline is not delivering better medicines

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Despite the large number of new medicines entering the market every year, the vast majority offer few clinical advantages for patients over existing alternatives. Governments and pharmaceutical companies share the responsibility for this innovation deficit in the sector.

Many in the pharmaceutical sector suggest that the industry is suffering from a crisis, driven by a rise in the cost of developing drugs. Industry analysts fret that financial rewards are no longer sufficient for companies to maintain the historical rates of investment needed to develop clinically useful medications.¹ Despite these concerns, regulators in the US and Europe granted marketing authorizations to a record number of new medicines in 2014. In this article, we consider the industry's recent innovativeness and show that the majority of new medicines offer few clinical advantages over existing alternatives. We discuss how both government and pharmaceutical company practices contribute to the ongoing innovation deficit in the sector. To the extent that pharmaceutical companies have a disproportionate emphasis on marketing versus research, governments fail to correct this imbalance by sending coordinated and consistent policy signals to the industry.

A paucity of clinically superior medicines

Ideally, pharmaceutical companies develop new treatment alternatives for conditions with no current (satisfactory) remedies or drugs that offer meaningful therapeutic improvement over existing options. Over the past half century, the pharmaceutical industry has been responsible for the development of innovative medicines: significant products that transformed the management and treatment of diseases.² In recent years, however, industry analysts have adopted several alternative definitions to measure innovation.³ These include, among others, pharmacological improvements related to the kinetic properties of new medicines. Today, what innovation means depends on the particular metric used to evaluate it (**Table 1**). Some of the commonly used definitions significantly deviate from the way innovation is understood by patients and clinicians: as new medicines that significantly improve health when compared to older alternatives.

Currently, the most common approach to measure innovation is to count the number of new drug approvals.³ The number of drug approvals has increased over the past five decades, culminating in 41 approvals in the US and 40 in Europe in 2014 alone, as compared to a 50-year average of 20 approvals per year.^{4,5} Large numbers of new drugs in recent years have been taken as a proxy for the innovative capacity of the industry.

Unfortunately, the recent increase in the numbers of new drugs is not necessarily indicative of new breakthroughs; instead, it largely reflects continued market entry of modest, relatively minor modifications of existing drugs.⁶ Studies published over the past decades evaluating the clinical importance of new drugs consistently report a negative trend.⁷⁻¹¹ Regardless of differences in analytic approach and time period, these studies unequivocally characterize only a minority of new drugs as clinically superior to existing alternatives.³ According to Luijn, approximately 10% of 122 new medicines that entered the European market between 1999 and 2005 were deemed superior to drugs already on offer.¹² Among the set of drugs reviewed by German authorities between 2012 and 2013, approximately 20% were concluded to offer significant benefit compared to existing alternatives and none were deemed to offer major benefit.¹³ Between 1990 and 2003, only 6% of 1147 drugs approved in Canada provided a substantial improvement over existing drug products.¹⁴ Canadian authorities considered 10% of new drugs approved between 2004 and 2009 as highly innovative.¹⁵

Despite the paucity of clinically superior drugs, the size of the pharmaceutical market grew by a factor of 2.5 in real terms between 1990 and 2010 (**Figure 1**). Although recent estimates are not available, much of the increase in pharmaceutical expenditures has been due to the increasing investment in me-too medicines, rather than the small minority of clinically superior medications.¹⁴ During a period when the share of health expenditures attributable to pharmaceuticals consistently increased and medication affordability suffered,^{16,17} pharmaceutical companies have remained profitable. Over the last 30 years, firms lost their number one position in the Fortune 500 only in 2003, coming third behind oil and financial companies. In 2012, the top five pharmaceutical companies included in the Fortune 500 earned over \$50 billion in net profits.

Inconsistent and unpredictable government regulations

Substantial accountability for the innovation deficit in the sector rests with governments. A unique aspect of the pharmaceutical industry is the scope of regulations surrounding its practices. Such regulations have ensured that products entering the market are efficacious and safe, according to data from rigorous trials. These same regulations should also foster research, development, and access to innovative drugs and yet it is clear that regulatory agencies responsible for approving the market entry of new medications such as the FDA and EMA are reluctant to send the correct signals to pharmaceutical companies. For example, regulators still do not require comparative trials for me-too agents entering drug classes with multiple effective agents.¹⁸

Regulators in recent years have in fact progressively lowered their evidence requirements for market entry of new drugs by requiring smaller trials, surrogate endpoints, and placebo comparisons, and increasingly adopted expedited approvals.^{19,20} Such rushed approvals had significant implications for drug safety.^{21,22} Several regulatory designations are aimed at shortening the timeline for regulatory review with the ultimate goal of making drugs available as rapidly as possible. A significant unintended consequence of this regulatory enthusiasm for fast market access of new drugs has been an estimated 35% increase in safety warnings and market withdrawals, with over one fourth of drugs approved since 1992 receiving black-box warnings or being withdrawn from the market.²³ Raising the bar for market entry of new drugs, particularly those in established areas, would serve as a disincentive to invest in crowded areas, and encourage companies to concentrate on developing clinically superior drugs.⁵

Regulatory demands may even run counter to facilitating the development of better medicines. Inconsistency and unpredictability of expectations across international borders adds significant complexity to research and development (R&D) efforts in today's global market. Notably, health technology assessment bodies, which serve as barriers to market entry in several countries, have varying evidence expectations and employ different methods for different settings.²⁴ These bodies do not have a unified perception of benefit and value, and disagree on what constitutes clinical superiority. This means that firms need to tailor their drug applications on a market-by-market basis, often using expensive, local contractors, and are unable to find economies of scale for approval activities. In the end, a particular drug may be covered in one setting but not in another, with substantial disparities in the recommendations issued for new drugs across countries with similar GDP per capita and health spending levels.²⁵

In recent years, government funding for research has stagnated (and indeed declined) and it has correlated only marginally with disease burden.²⁶ Current levels of government funding for research disproportionately prioritize cancer over other conditions that are associated with significantly higher burden of disease. Although such research investments have materialized in new product launches over the past decade, they brought modest therapeutic benefits. Of 71 oncology products approved between 2002 and 2014, the median gain in overall survival was 2.1 months.²⁷

An unintended consequence of government regulations has been a significant expansion of the pharmaceutical market over the past decades. Policies aimed at increasing generic drug use have indirectly contributed to the industry's financial success by continuing to reward me-too drugs rather than clinically superior medicines. Following the enactment of the Waxman-Hatch Act in the US in 1984, and accompanied by European measures to improve generic prescribing, use of generic products has risen.²⁸ In the US, a large share of prescriptions is now for generics, with over \$113 billion of sales substituted with generic alternatives due to patent expirations between 2010 and 2014. In the absence of coordinated mechanisms to identify and reward better medicines, generics have provided the fiscal space for governments to purchase expensive patented products despite the lack of evidence that brand formulations are better than older and cheaper alternatives. Indeed, cost reductions achieved by generic use were more than offset by increasing expenditure in expensive branded medications. In 2013, although generics accounted for over 70% of all prescription drugs used in the US, they were responsible for less than 30% of total drug spending. Branded formulations, on the other hand, accounting for only 30% of medications, were responsible for 70% of expenditures.²⁹ In Europe, although generics make up almost half of volume sales, they represent less than 20% of value sales.³⁰

Industry's disproportionate emphasis on marketing versus research

The pharmaceutical industry shares the responsibility for the paucity of clinically superior medicines entering the market. Firms operate in a unique environment shaped by the risky nature of drug discovery; fewer than one in ten molecules that enter development receive approval after an average development period of 13.5 years.³¹ To minimize risk, industry continues to invest heavily in already established areas and has a disproportionate emphasis on marketing versus research.

In the short-term, firms are under pressure to demonstrate value to their shareholders,^{32,33} whose short-term interests may be at odds with the longer-term objectives of clinicians, patients and policy makers seeking improvements in health. Industry's short-term goals encourage research on me-too products in established areas, which provide more reliable returns on

investment at the potential expense of breakthroughs in other areas and in breach of the implicit contract between firms and society.

More than one drug alternative may be warranted in some therapeutic areas to allow for patient-centred, individualised treatment options; however the industry's overreliance on me-too drugs (there are >5 statins; >15 beta-blockers; and >30 anti-diabetics) cannot always be justified – particularly when they do not offer demonstrable quality of life, convenience, or therapeutic benefits in different patient sub-groups.

In recent years, several large companies have allocated a disproportionate share of R&D expenses to late-stage development of drug candidates while neglecting pre-clinical discovery.^{31,34} These reorganisations naturally led R&D operations away from science-driven investigation to process-led development (**Box 1**).

High profits in the pharmaceutical sector are not necessarily linked to better products.^{35,36} Instead, it is the industry's emphasis on marketing³⁷ – disproportionately high compared to its research efforts⁶ – that drives prescriber and patient behaviour.³⁸ Companies spend almost twice as much on promotion as they do on R&D.³⁹ A hallmark of the marketing policy is firms' ability to exert direct influence on professionals' decisions⁴⁰ and, in the US, on health consumers through direct to consumer advertising.⁴¹

The industry understands that its sales and marketing strategy matters as much as (if not more than) its ability to develop clinically superior medicines.³⁹ Particularly evident in lucrative drug classes, firms' marketing strategies successfully change prescribing behaviors. A now classic example of this is in the statin market. Until recently, an intensive marketing campaign helped to ensure that the utilization rates of five statins trailed behind those of atorvastatin, despite the lack of comparative evidence for its superiority to existing alternatives such as simvastatin.⁴² Sustained marketing of atorvastatin, even with cheaper generics available, has helped it become the best-selling medication in history.⁴³ Similarly, a successful marketing campaign for esomeprazole, a repackaged version of an older product, generated over \$35 billion in revenue between 2006 and 2013.⁴⁴

Way forward

Improving the drug development process will require a reconfiguration of system-wide incentives. Collective, concerted regulatory action is needed to send the correct signals to pharmaceutical companies. Policy options are several and include the identification of priority therapeutic areas for which R&D could be made more economically attractive. In other areas such as antibiotics, public-private partnerships, advance market commitments, extended marketing exclusivity or risk-sharing policies could be designed to share the risk of financing early-stage research. To encourage competition and deter industry-wide consolidation, governments could more closely monitor monopolistic behavior in certain therapeutic areas.

Finally, pricing and reimbursement policies should reward clinically superior medicines and not me-too drugs.⁵⁴ Current spending on me-too medications distorts the calculus of industry's R&D activity. By preferentially reimbursing drugs that offer clinically meaningful improvements over existing alternatives, governments could encourage true breakthroughs.⁵⁵ Countries should send a coordinated signal to the industry independently of their differing approaches to regulation. Instituting stricter evidence requirements at the time of market entry and requiring evidence of clinical effectiveness in robust trials would be an important first step.

Conclusion

Patients and clinicians are faced with a paucity of clinically superior medicines. In a convoluted global policy environment where regulatory structures coax firms to engage in innovative sales and marketing practices rather than in innovative science, future efforts should focus on streamlining the policy environment surrounding the industry and reward the development of clinically superior medicines.

Key Messages

- Government practices contribute to the innovation deficit in the pharmaceutical sector: low bar for market entry of new products; stagnating investment in R&D; and inconsistency and unpredictability of regulatory expectations and incentive structures across international borders.
- Industry practices share the responsibility for the paucity of clinically superior drugs: disproportionate emphasis on marketing versus research; continued investment in already established areas; and a declining appetite for risky research.
- Concerted regulatory action is needed at the international level to incentivize and reward the development of clinically superior medicines, not me-too drugs.

Contributors and sources

All authors are actively engaged in academic research on the pharmaceutical sector. HN and EM have written several articles on pharmaceutical policy and regulation in the EU and the US. EM has extensive experience of European health systems and regulatory policies through his involvement with the European Observatory on Health Systems and Policies. EM, HN, and AC devised the article. HN and AC wrote the first draft. EM contributed to subsequent drafts. All have read and agreed to the final version. HN is guarantor.

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Conflicts of Interest

We declare no conflicts of interest.

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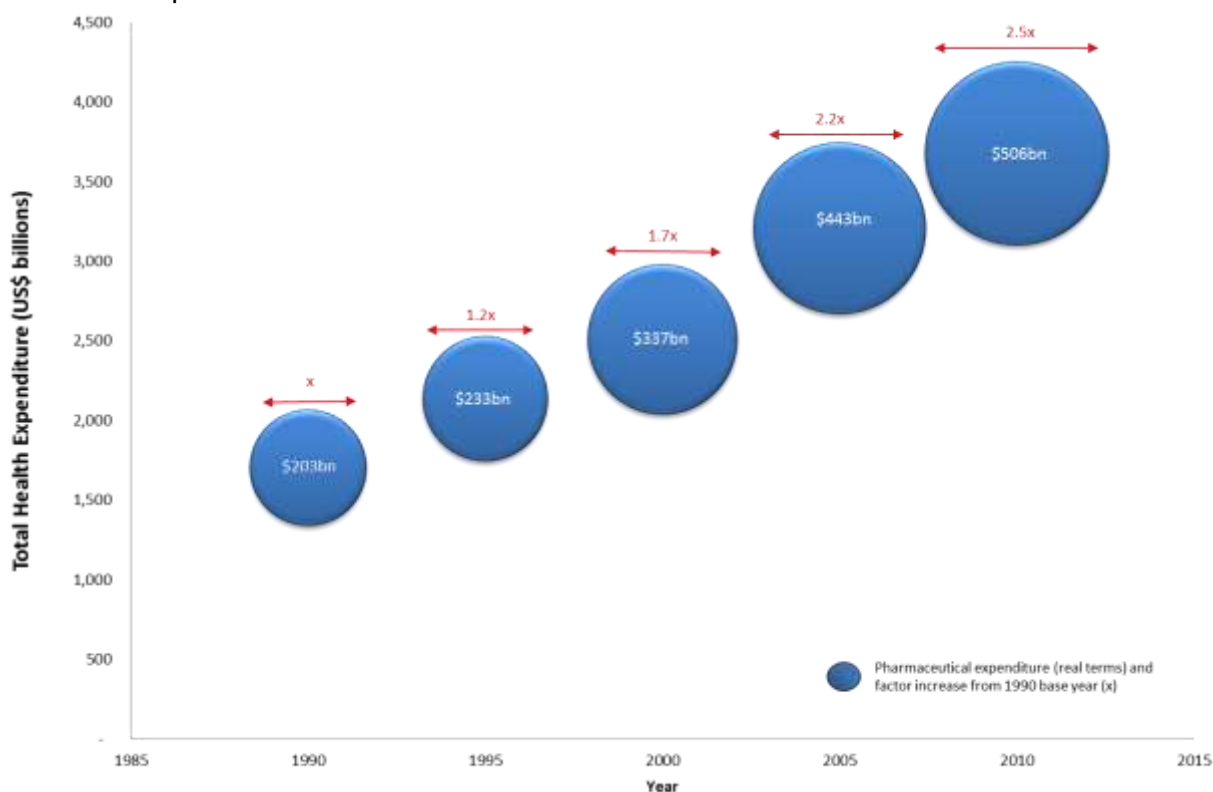
Table 1. Primary categories of measures used to define and evaluate innovation in the pharmaceutical sector

Category	Description
Number of new drug approvals	In a recent systematic review of the literature, Kesselheim and colleagues identified drug counts as the most common metric used to evaluate the innovativeness of the pharmaceutical sector. ¹ Regulators (e.g., Food and Drug Administration and European Medicines Agency), pharmaceutical companies and policymakers often refer to the number of new drug approvals to indicate the health of the pharmaceutical research and development pipeline. ²
Technological and pharmacological novelties	Studies evaluating innovation on the basis of therapeutic and pharmacological characteristics of new medicines often focus on pharmacokinetic novelties, which may or may not be associated with clinical improvements. ^{3,4}
Number of patents associated with new medicines	As a measure of innovativeness, researchers previously investigated the number of patents granted to new medicines and the number of subsequent citations of such patents. ⁵
Degree of clinical superiority of new medicines over existing alternatives	Patients, clinicians, and wider society often equate new with better, and expect new medicines to be clinically superior to existing alternatives in terms of important and relevant outcomes. Studies evaluating innovation in terms of clinical superiority used various surrogate, clinical, quality-of-life, and safety endpoints to measure the extent to which new medicines offer advantages over older alternatives. ⁶⁻¹⁰

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Figure 1. Growth in total health care expenditures and concurrent pharmaceutical drug expenditures in selected OECD countries between 1990 and 2010. Pharmaceutical expenditure growth is also presented as annual factor increases ^{a,b,c,d}



Notes: ^a Real* growth in total health expenditure (US\$ billions, PPP) and annual factor increase from 1990 (baseline) in pharmaceutical expenditure, as denoted by bubble size, between 1990 and 2010 (5 year periods) for selected OECD countries: Australia, Canada, Finland, Germany, Greece, Iceland, Italy, Netherlands, Sweden, Switzerland, United Kingdom, United States.

^b Real pharmaceutical expenditures (US\$ billions, PPP) are provided within bubbles.

^c Sources: Authors' own analysis based on OECD Health Database, 2014 for Australia, Finland, Germany, Greece, Iceland, Italy, Netherlands, Sweden, Switzerland, and United Kingdom. Source for Canada: the Canadian Institute for Health Information, 2013. Sources for United States: Catlin et al. (2007) and Martin et al. (2012), years 1991-2005 (excl. 1990, 2000) and 1990, 2000, 2007-2010, respectively.

^d Greece: Total health expenditure data for 2008 obtained from WHO National Health Accounts Database, 2014. Pharmaceutical expenditure data used for 2010 is next nearest year, 2011.

* Deflated at average rate of 2.4% for all years (2011 base year)

Sources for the United States:

Catlin A, Cowan C, Heffler S, Washington B. National health spending in 2005: the slowdown continues. Health affairs (Project Hope). Jan-Feb 2007;26(1):142-153.

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Box 1. New Big Pharma: Industry's declining appetite for risky research

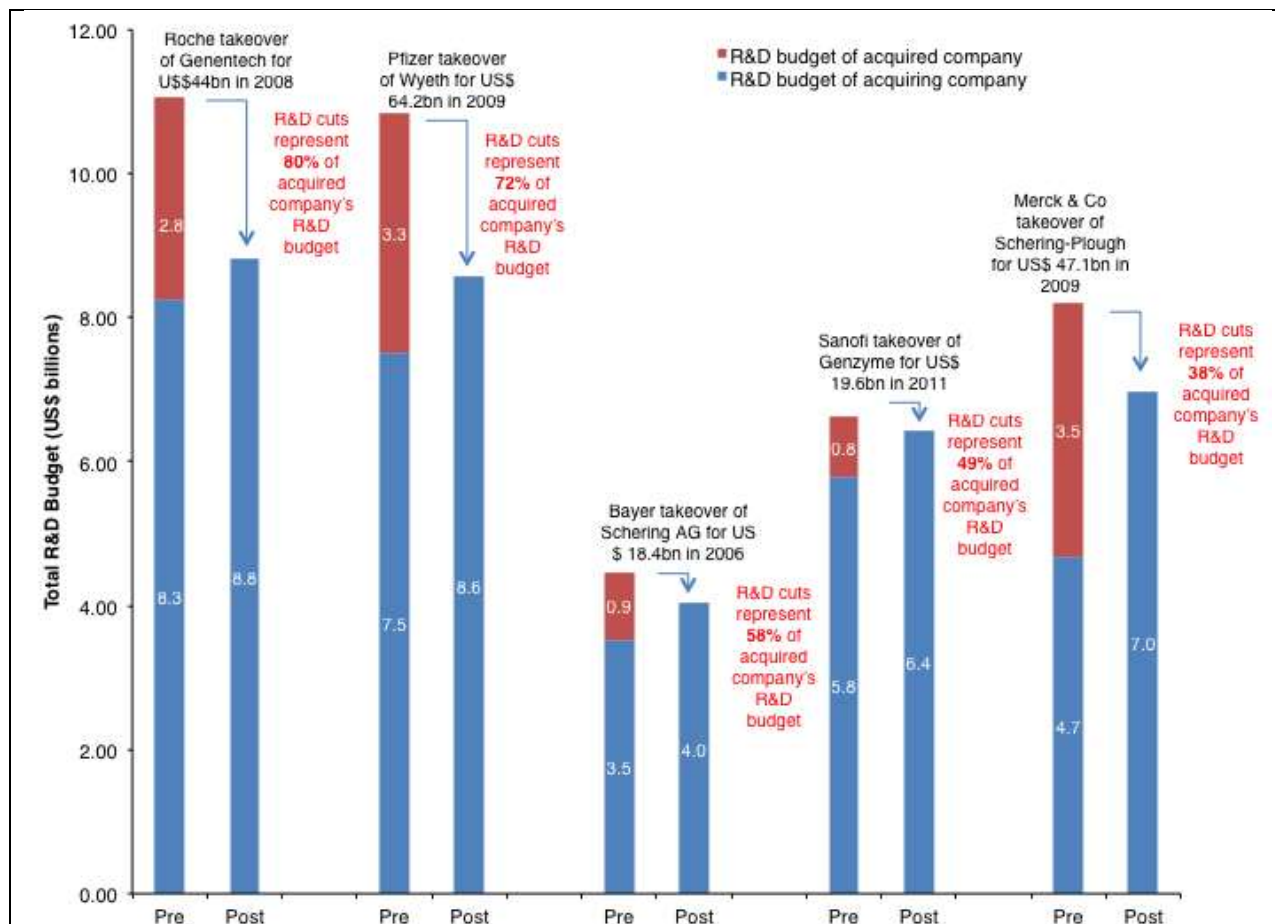
A recent analysis showed that the total number of scientific publications by large pharmaceutical companies declined while the number of external collaborations increased.⁴⁵ Firms are increasingly outsourcing their R&D operations and creating partnerships for more beneficial risk-sharing, cost reduction and to optimize the clinical trial process.

The shift away from science-driven investigation to process-led drug development highlights the industry's declining appetite for risky drug discovery. This new business model is focused on identifying, acquiring, and promoting promising molecules created by smaller firms that are often financed by public funds.⁴⁶

Many large pharmaceutical firms increasingly resort to acquiring promising drug candidates from smaller competitors that have products in late-phase development.³¹ Hence, underperforming companies – firms with a high 'desperation index'⁴⁷ – are increasingly "buying drugs on Wall Street rather than in the research lab."^{48,49} By acquiring development pipelines in familiar areas, companies are able to secure a steady stream of short-term revenues from promising drugs.

The pervasive belief that consolidation equates to the development of clinically superior medicines is not backed by either theory or evidence.⁵⁰ Economic theory suggests that decreasing the number of companies would decrease competition, in turn impeding individual firms' capacity to develop clinically superior drugs. Cuts in R&D investment following such mergers and acquisitions (**Figure**), which are often aimed at achieving efficiency and economies of scale, result in the loss of two essential conditions for breakthroughs: the existence of independent research groups (fewer researchers now work in laboratories) and diverse R&D portfolios.⁵¹ The resulting loss of the "parallel paths"⁵² of research – the pursuit of multiple approaches to addressing the same research question⁵³ – leads to a reduction in the number of breakthrough drugs that reach patients.

Figure. Reductions in R&D budgets after acquisition as a percent of the acquired company's R&D budget before acquisition. Figure shows the R&D reductions for the five largest acquisitions since 2005, ordered according to the percentage reduction of R&D.



Notes: Author's analysis using DataStream 5.1 (Thomson Reuters).

"Pre" denotes the research and development budgets (in US\$ billions) of acquired and acquiring companies during the year before the takeover. "Post" denotes the research and development budget (in US\$ billions) of the combined company during the year following the takeover. All costs are in 2010 US\$, adjusted using CPI (available on <http://data.bls.gov/cgi-bin/cpicalc.pl>)

Sensitivity analysis evaluated taking the average of the research and development budgets for two years following the acquisition, which did not change the overall figure materially. Another sensitivity analysis evaluated the counterfactual research and development budgets of separate companies if they did not merge, assuming that the linear rate of budget growth in the five years prior to the acquisition would continue during the year of the deal making.