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ANALYSIS

Why the drug development pipeline is not delivering better medicines

Despite the large number of new medicines entering the market every year, few offer important clinical advantages for patients. **Huseyin Naci**, **Alexander Carter**, and **Elias Mossialos** explain the reasons for this innovation deficit and offer some solutions

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Many in the pharmaceutical sector suggest that the industry is in crisis. Industry analysts fret that financial rewards are no longer sufficient for companies to maintain the investment needed to develop clinically useful drugs.[1] Despite these concerns, regulators in the US and Europe granted marketing authorisations to a record number of new medicines in 2014. However, the majority of new medicines offer few clinical advantages over existing alternatives. We discuss how both government and drug company practices contribute to the ongoing innovation deficit in the sector.

Paucity of clinically superior medicines

Patients and clinicians commonly understand innovation to mean a medicine that has transformed management and treatment,[2] either by providing treatments for conditions with no current (satisfactory) remedies or by offering meaningful improvement over existing options. In recent years, however, industry analysts have adopted other definitions to measure innovation (box 1).[3] 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; this compares with a 50 year average of 20 approvals a year.[4 5]

Large numbers of new drugs have been taken as a proxy for the innovative capacity of the industry. Unfortunately, rather than new breakthroughs, most of the new drugs are relatively minor modifications of existing treatments.[6] Studies evaluating the clinical importance of new drugs over the past decades consistently report a negative trend.[7-11] Regardless of differences in analytical approach and time period, all characterise only a minority of new drugs as clinically superior to existing alternatives.[3] Luijn found that 10% of 122 new medicines on the European market between 1999 and 2005 were superior to drugs already on offer.[12] Among drugs reviewed by German authorities between 2012 and 2013, about 20% were concluded to offer some benefit over existing alternatives and none was 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] and Canadian authorities considered 10% of new drugs approved between 2004 and 2009 as highly innovative.[15]

Despite the paucity of clinically superior drugs, the pharmaceutical market grew by a factor of 2.5 in real terms between 1990 and 2010 (fig 1⇓). Much of the increased expenditure on drugs was the result of increasing industry investment in "me-too" medicines rather than clinically superior medications.[14] Drug companies have remained profitable over this period while the proportion of health spending on drugs has increased and drugs have become less affordable.[16 17] Over the past 30 years, firms lost their number one position in the Fortune 500 ranking of US companies only in 2003, coming third behind oil and financial companies. In 2012, the top five pharmaceutical companies included in the Fortune 500 earned over $50bn (£30bn; €40bn) in net profits.

Inconsistent and unpredictable government regulations

Substantial accountability for the innovation deficit in the sector rests with governments. The industry is highly regulated to ensure that products entering the market are efficacious and safe. These same regulations should also foster research, development, and access to innovative drugs, and yet regulatory agencies responsible for approving new medications such as the Food and Drug Administration and European Medicines Agency seem reluctant to send the correct signals to drug companies. For example, regulators do not require comparative trials for me-too drugs in classes with multiple effective agents.[23]

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Box 1: Measures of innovation

Number of new drug approvals—used by regulators, drug companies, and policy makers

Technological and pharmacological novelties—for example, changes in pharmacokinetic properties that may or may not be clinically relevant

Number of patents associated with new medicines—used alone or together with citations of new patents

Clinical superiority over existing alternatives—increasingly measured using surrogate endpoints rather than outcomes relevant to patients

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. They have also increasingly adopted expedited approvals to get new drugs on to the market quicker.[24 25] Such rushed approvals had important implications for drug safety.[26 27] There has been an estimated 35% increase in safety warnings and market withdrawals, with over a quarter of drugs approved since 1992 receiving black box warnings or being withdrawn from the market.[28] Raising the bar for market entry of new drugs would be a disincentive to invest in crowded areas and encourage companies to concentrate on developing clinically superior drugs.[5]

Regulatory demands may even hinder the development of better medicines. Inconsistency and unpredictability of expectations across international borders add to the complexity of research and development efforts in today's global market. Notably, health technology assessment bodies, which determine funding of treatment in several countries, have varying evidence expectations and use different methods.[29] These bodies do not have a unified perception of benefit and value, and disagree on what constitutes clinical superiority. Companies therefore have to tailor their drug applications to each market, often using expensive local contractors, and a particular drug may end up being covered in one country but not another. Substantial disparities exist in the recommendations issued for new drugs across countries with similar economic characteristics.[30]

Another problem is that, in recent years, government funding for research has stagnated (and indeed declined) and has correlated only marginally with disease burden.[31] US government funding for research disproportionately prioritises cancer over other conditions associated with much higher burdens of disease. Although such research investments have resulted in new products 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.[32]

An unintended consequence of government regulations has been a large expansion of the pharmaceutical market. Policies aimed at increasing generic drug use have indirectly contributed to the rise of me-too drugs. Generics now account for a large share of prescriptions, with over $113bn of US sales substituted with generic alternatives between 2010 and 2014.[33] 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 lack of evidence that they are better than older and cheaper alternatives. Indeed, cost reductions achieved by generic use were more than offset by increasing expenditure on 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.[34] In Europe, although generics make up almost half of volume sales, they represent less than 20% of value sales.[35]

Industry's disproportionate emphasis on marketing

The pharmaceutical industry shares the responsibility for the paucity of clinically superior medicines entering the market. Companies operate in a unique environment shaped by the risky nature of drug discovery; fewer than one in 10 molecules that enter development receive approval after an average development period of 13.5 years.[36] To minimise risk, industry invests heavily in already established areas and has a disproportionate emphasis on marketing compared with research.

In the short term, firms are under pressure to demonstrate value to their shareholders,[37 38] whose interests may be at odds with the longer term objectives of clinicians, patients, and policy makers. This encourages research on me-too products, 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. Although multiple drugs may be warranted to allow for individualised, patient centred treatment, the industry's over-reliance on me-too drugs (there are more than five statins, over 15 β blockers, and over 30 antidiabetic drugs) cannot always be justified, especially if they do not offer demonstrable quality of life, convenience, or therapeutic benefits to different patient subgroups.

In recent years, several large companies have allocated a disproportionate share of research and development budgets to late stage development of drug candidates while neglecting preclinical discovery.[36 39] These reorganisations naturally led research and development operations away from science driven investigation to process led development (box 2).

High profits in the pharmaceutical sector are not necessarily linked to better products.[47 48] Instead, it is marketing that drives prescriber and patient behaviour and therefore industry profits.[49] Companies spend almost twice as much on promotion as they do on research and development.[50] An intensive marketing campaign helped atorvastatin become the best selling medication in history[51] despite lack of comparative evidence for its superiority to cheaper generic alternatives such as simvastatin.[52] Similarly, a successful marketing campaign for esomeprazole, a repackaged version of an older product, generated over $35bn in revenue between 2006 and 2013.[53]

Way forward

Improving the drug development process will require collective, concerted regulatory action to send the correct signals to drug companies. Policy options include identifying priority therapeutic areas and making research in them more economically attractive. This could be through public-private partnerships, advance market commitments, extended marketing exclusivity, or policies to share the risk of financing early stage research. To encourage competition and deter industry-wide consolidation, governments could more closely monitor takeovers.

Finally, pricing and reimbursement policies should reward clinically superior medicines and not me-too drugs.[43] By

Box 2: How mergers and acquisitions reduce innovation

Drug companies are increasingly outsourcing their research and development and creating partnerships to reduce their risks and costs and optimise the clinical trial process.[40] This new business model is focused on identifying, acquiring, and promoting promising molecules created by smaller firms that are often financed by public funds.[36 41] By acquiring development pipelines in familiar areas, companies are able to secure a steady stream of short term revenues from promising drugs. Hence, underperforming companies are increasingly "buying drugs on Wall Street rather than in the research lab."[42 43]

The pervasive belief that consolidation equates to the development of clinically superior medicines is not backed by theory or evidence.[44] Economic theory suggests that decreasing the number of companies would decrease competition, in turn impeding capacity to develop clinically superior drugs. Cuts in research and development investment after such mergers and acquisitions (fig 2⇓), which are often aimed at achieving efficiency and economies of scale, result in the loss of two essential conditions for breakthroughs: independent research groups (fewer researchers now work in laboratories) and diverse research portfolios.[45] The resulting loss of multiple approaches to the same research question[46] leads to a reduction in the number of breakthrough drugs that reach patients.

preferentially reimbursing drugs that offer clinically meaningful improvements over existing alternatives, governments could encourage true breakthroughs.[54] Countries should send a coordinated signal to the industry independently of their differing approaches to regulation. Stricter evidence requirements at the time of market entry and requiring evidence of clinical effectiveness in robust trials would be important first steps.

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Key messages

- The innovation deficit in the pharmaceutical sector arises from a combination of government and industry practices
- A low bar for market entry of new products, stagnating government investment in research, and inconsistency in international regulations discourage innovation
- Industry puts a disproportionate emphasis on marketing versus research and prefers continued investment in established areas to risky research
- Concerted regulatory action is needed at the international level to reward the development of clinically superior medicines

Figures

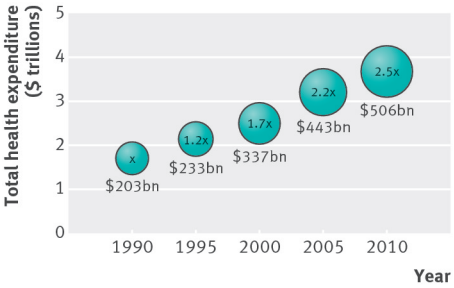

Fig 1 Growth in total healthcare expenditure and drug expenditure (represented by size of bubbles) in selected countries (Australia, Canada, Finland, Germany, Greece, Iceland, Italy, Netherlands, Sweden, Switzerland, United Kingdom, and United States) between 1990 and 2010 (analysis details are available from the authors)[18-22]

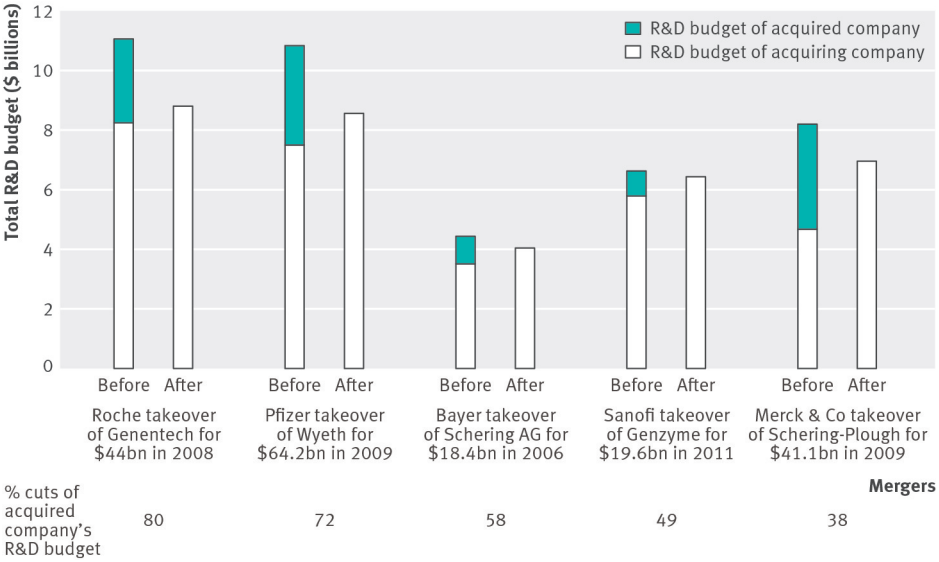

Fig 2 Reductions in research and development (R&D) budgets after acquisition as percentage of acquired company's R&D budget before acquisition. All costs are in 2010 $, adjusted using consumer price index. Source: Thomson Reuters DataStream 5.1. Analysis details are available from the authors