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ANALYSIS

Pharmaceutical research and development: what do we get for all that money?

Data indicate that the widely touted "innovation crisis" in pharmaceuticals is a myth. The real innovation crisis, say **Donald Light** and **Joel Lexchin**, stems from current incentives that reward companies for developing large numbers of new drugs with few clinical advantages over existing ones

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Since the early 2000s, industry leaders, observers, and policy makers have been declaring that there is an innovation crisis in pharmaceutical research. A 2002 front page investigation by the *Wall Street Journal* reported, "In laboratories around the world, scientists on the hunt for new drugs are coming up dry . . . The $400 billion a year drug industry is suddenly in serious trouble."[1] Four years later, a US Government Accounting Office assessment of new drug development reported that "over the past several years it has become widely recognized throughout the industry that the productivity of its research and development expenditures has been declining."[2] In 2010, Morgan Stanley reported that top executives felt they could not "beat the innovation crisis" and proposed that the best way to deal with "a decade of dismal R&D returns" was for the major companies to stop trying to discover new drugs and buy into discoveries by others.[3] Such reports continue and raise the spectre that the pipeline for new drugs will soon run dry and we will be left to the mercies of whatever ills befall us.[4]

The "innovation crisis" myth

The constant production of reports and articles about the so called innovation crisis rests on the decline in new molecular entities (defined as "an active ingredient that has never been marketed . . . in any form"[5]) since a spike in 1996 that resulted from the clearance of a backlog of applications after large user fees from companies were introduced (fig 1⇓). This decline ended in 2006, when approvals of new molecular entities returned to their long term mean of between 15 and 25 a year (fig 2⇓).[6] Even in 2005, an analysis of the data by a team at Pfizer concluded that the innovation crisis was a myth "which bears no relationship to the true innovation rates of the pharmaceutical industry."[7] So why did the claims and stories not abate?

A subsequent analysis also concluded that the innovation crisis was a myth and added several insights.[8] Based on US Food and Drug Administration records, Munos found that drug companies "have delivered innovation at a constant rate for almost 60 years." The new biologicals have been following the same pattern "in which approvals fluctuate around a constant, low level."[8] These data do not support frequently heard complaints about how hard it is to get any new drug approved. They also mean that neither policies considered to be obstacles to innovation (like the requirement for more extensive clinical testing) nor those regarded as promoting innovation (like faster reviews) have made much difference. Even the biotechnology revolution did not change the rate of approval of new molecular entities, though it changed strategies for drug development.[9] Meanwhile, telling "innovation crisis" stories to politicians and the press serves as a ploy, a strategy to attract a range of government protections from free market, generic competition.[10 11]

The real innovation crisis

More relevant than the absolute number of new drugs brought to the market is the number that represent a therapeutic advance. Although the pharmaceutical industry and its analysts measure innovation in terms of new molecular entities as a stand-in for therapeutically superior new medicines, most have provided only minor clinical advantages over existing treatments.

The preponderance of drugs without significant therapeutic gains dates all the way back to the "golden age" of innovation. Out of 218 drugs approved by the FDA from 1978 to 1989, only 34 (15.6%) were judged as important therapeutic gains.[12] Covering a roughly similar time period (1974-94), the industry's Barral report on all internationally marketed new drugs concluded that only 11% were therapeutically and pharmacologically innovative.[13] Since the mid-1990s, independent reviews have also concluded that about 85-90% of

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all new drugs provide few or no clinical advantages for patients.[14-19]

This small, steady increase in clinically superior drugs contrasts with the FDA granting "priority" review status to 44% of all new drugs from 2000 to 2010.[20] The percentage of drugs with a priority designation began to increase in 1992 when companies started funding the FDA's approval process. Other regulatory agencies have classified far fewer of the same medicines as needing accelerated reviews.[21] Post-market evaluations during the same period are much less generous in assigning significant therapeutic advances to medications.[18 21]

This is the real innovation crisis: pharmaceutical research and development turns out mostly minor variations on existing drugs, and most new drugs are not superior on clinical measures. Although a steady stream of significantly superior new drugs enlarges the medicine chest from which millions benefit, medicines have also produced an epidemic of serious adverse reactions that have added to national healthcare costs.[22]

How much does research and development cost?

Although the pharmaceutical industry emphasises how much money it devotes to discovering new drugs, little of that money actually goes into basic research. Data from companies, the United States National Science Foundation, and government reports indicate that companies have been spending only 1.3% of revenues on basic research to discover new molecules, net of taxpayer subsidies.[23] More than four fifths of all funds for basic research to discover new drugs and vaccines come from public sources.[24] Moreover, despite the industry's frequent claims that the cost of new drug discovery is now $1.3bn (£834m; €1bn),[25] this figure, which comes from the industry supported Tufts Center,[26] has been heavily criticised. Half that total comes from estimating how much profit would have been made if the money had been invested in an index fund of pharmaceutical companies that increased in value 11% a year, compounded over 15 years.[26] While used by finance committees to estimate whether a new venture is worth investing in, these presumed profits (far greater than the rise in the value of pharmaceutical stocks) should not be counted as research and development costs on which profits are to be made. Half of the remaining $0.65bn is paid by taxpayers through company deductions and credits, bringing the estimate down to one quarter of $1.3bn or $0.33bn.[27] The Tufts study authors report that their estimate was done on the most costly fifth of new drugs (those developed in-house), which the authors reported were 3.44 times more costly than the average, reducing the estimate to $90m. The median costs were a third less than the average, or $60m. Deconstructing other inflators would lower the estimate of costs even further.

Hidden business model

How have we reached a situation where so much appears to be spent on research and development, yet only about 1 in 10 newly approved medicines substantially benefits patients? The low bars of being better than placebo, using surrogate endpoints instead of hard clinical outcomes, or being non-inferior to a comparator, allow approval of medicines that may even be less effective or less safe than existing ones. Notable examples include rofecoxib (Vioxx), rosiglitazone (Avandia), gatifloxacin (Tequin), and drotrecogin alfa (Xigris).

Although the industry's vast network of public relations departments and trade associations generate a large volume of stories about the so called innovation crisis, the key role of blockbuster drugs, and the crisis created by "the patent cliff,"[28] the hidden business model of pharmaceuticals centres on turning out scores of minor variations, some of which become market blockbusters. In a series of articles Kalman Applbaum describes how companies use "clinical trial administration, research publication, regulatory lobbying, physician and patient education, drug pricing, advertising, and point-of-use promotion" to create distinct marketing profiles and brand loyalty for their therapeutically similar products.[29] Sales from these drugs generate steady profits throughout the ups and downs of blockbusters coming off patents. For example, although Pfizer lost market exclusivity for atorvastatin, venlafaxine, and other major sellers in 2011, revenues remained steady compared with 2010, and net income rose 21%.[30]

Applbaum contends that marketing has become "the enemy of [real] innovation."[31] This perspective explains why companies think it is worthwhile paying not only for testing new drugs but also for thousands of trials of existing drugs in order to gain approval for new indications and expand the market.[32] This corporate strategy works because marketing departments and large networks of sponsored clinical leaders succeed in persuading doctors to prescribe the new products.[33] An analysis of Canada's pharmaceutical expenditures found that 80% of the increase in its drug budget is spent on new medicines that offer few new benefits.[16] Major contributors included newer hypertension, gastrointestinal, and cholesterol drugs, including atorvastatin, the fifth statin on the Canadian market.

Myth of unsustainable research and development

Complementing the stream of articles about the innovation crisis are those about the costs of research and development being "unsustainable" for the small number of new drugs approved. Both claims serve to justify greater government support and protections from generic competition, such as longer data exclusivity and more taxpayer subsidies. However, although reported research and development costs rose substantially between 1995 and 2010, by $34.2bn, revenues increased six times faster, by $200.4bn.[25] Companies exaggerate costs of development by focusing on their self reported increase in costs and by not mentioning this extraordinary revenue return. Net profits after taxes consistently remain substantially higher than profits for all other Fortune 500 companies.[34]

This hidden business model for pharmaceutical research, sales, and profits has long depended less on the breakthrough research that executives emphasise than on rational actors exploiting ever broader and longer patents and other government protections against normal free market competition. Companies are delighted when research breakthroughs occur, but they do not depend on them, declarations to the contrary notwithstanding. The 1.3% of revenues devoted to discovering new molecules [23] compares with the 25% that an independent analysis estimates is spent on promotion,[35] and gives a ratio of basic research to marketing of 1:19.

Towards more cost effective, safer medicines

What can be done to change the business model of the pharmaceutical industry to focus on more cost effective, safer medicines? The first step should be to stop approving so many new drugs of little therapeutic value. The European Medicines Agency (EMA) does Europe a disservice by approving 74% of

all new applications based on trials designed by the companies, while keeping data about efficacy and safety secret.[36 37] Twenty nine per cent of new biologicals approved by the EMA received safety warnings within the first 10 years on the market,[38] and therapeutically similar drugs by definition have no advantages to offset their unknown risk of increased harm. We need to revive the Norwegian "medical need" clause that limited approval of new drugs to those that offered a therapeutic advantage over existing products.[39] This approach led to Norway having seven non-steroidal anti-inflammatory drugs on the market compared with 22 in the Netherlands.[40] Norway's medical need clause was eliminated in 1996 when it harmonised its drug approval process with that in the EU. EU countries are paying billions more than necessary for drugs that provide little health gain because prices are not being set to reward new drugs in proportion to their added clinical value.

We should also fully fund the EMA and other regulatory agencies with public funds, rather than relying on industry generated user fees, to end industry's capture of its regulator. Finally, we should consider new ways of rewarding innovation directly, such as through the large cash prizes envisioned in US Senate Bill 1137, rather than through the high prices generated by patent protection.[41] The bill proposes the collection of several billion dollars a year from all federal and non-federal health reimbursement and insurance programmes, and a committee would award prizes in proportion to how well new drugs fulfilled unmet clinical needs and constituted real therapeutic gains. Without patents new drugs are immediately open to generic competition, lowering prices, while at the same time innovators are rewarded quickly to innovate again. This approach would save countries billions in healthcare costs and produce real gains in people's health.

Contributors and sources: DWL is professor of comparative health care policy and has published several studies on pharmaceutical policy gathered at www.pharmamyths.net. For his work, he has been selected as a fellow at the Safra Center for Ethics at Harvard University for 2012-13. JRL is the author or coauthor of over 115 peer reviewed articles on all aspects of pharmaceutical policy. The authors made use of their knowledge from their individual and collaborative work on pharmaceutical economics including material from a variety of industry and government publications and their extensive personal libraries. DWL conceived, researched, and wrote the initial draft. JRL researched and revised, making substantial changes.

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The true crisis in pharmaceutical research

- The number of new drugs licensed remains at the long term average range of 15-25 a year
- However, 85-90% of new products over the past 50 years have provided few benefits and considerable harms
- The pharmaceutical industry devotes most research funds to developing scores of minor variations that produce a steady stream of profits
- Heavy promotion of these drugs contributes to overuse and accounts for as much as 80% of a nation's increase in drug expenditure
- Overinflated estimates of the average cost of research and development are used to lobby for more protection from free market competition

Figures

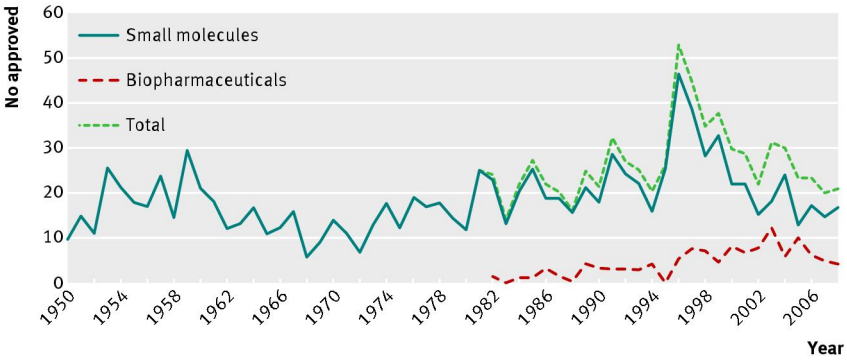

Fig 1 The innovation crisis starting in 1997 is a return to the long term average range of new approvals from an artificial spike caused by political factors[8]

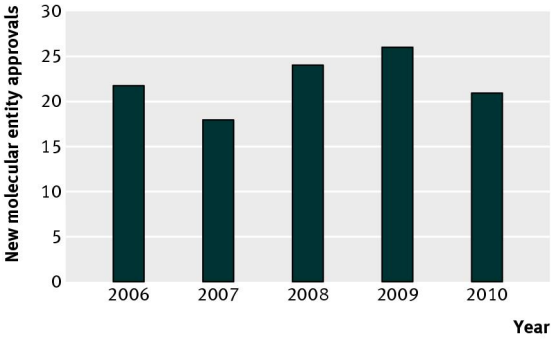

Fig 2 The rate of approval of new molecular entities returned to the long term average range by 2006