If you say something often enough, it must be true. Everyone knows that innovation is declining and is the source of all the woes of the pharmaceutical industry. But who has checked the facts?

Keynote review:

Is declining innovation in the pharmaceutical industry a myth?

Esther F. Schmid and Dennis A. Smith

Increasing the rate of innovation is a requirement to achieve much-needed advances in patient care, as well as to secure the future of the pharmaceutical industry. Currently, there is a perception in the external environment that pharmaceutical R&D is no longer innovative, fails to bring new drugs to market or, at best, produces a rising number of 'me-too' drugs with no advantage over existing treatments. In addition, the cost to discover and develop new medicines (i.e. cost per launch) has risen dramatically in recent years. The quoted development cost per medicine is a reality, and is not disputed here. However, data are provided that demonstrate that with regard to innovation rates, the current perception is wrong – although there have been, and continue to be, fluctuations in drug launches, there has been a steady increase in the number of new chemical entities launched, both in absolute numbers of FDA-approved medicines and in the proportion of priority reviews.

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For the past five years or so, the pharmaceutical industry has come under increasing scrutiny from analysts, shareholders, the media and patient groups, primarily as a result of the industry's perceived lack of innovation (www.nihcm.org/InnovationsPR.html). Most of the analyses that back the view of pharmaceutical companies as monoliths, unable to bring new medicines to market, have considered only a relatively short time span: between 1996 and 2004. This short time period should be contrasted with the 12–15 year period often needed to turn a scientific concept into a new chemical entity (NCE). We decided to investigate the industry's innovation record further and expanded the time period from 1945 to 2004, using FDA legacy data on approved NCEs and their categorization codes. The FDA categorization of priority reviews versus standard was used to identify drugs that at the

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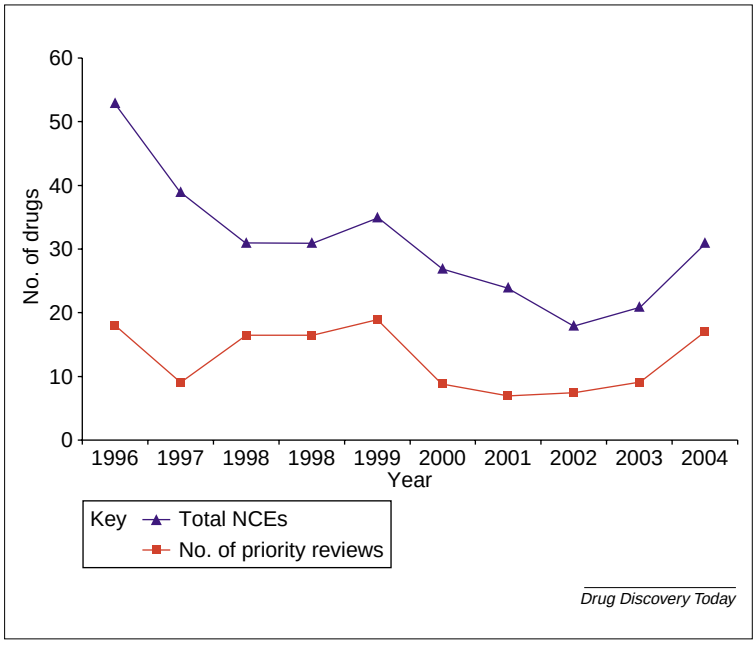

FIGURE 1

Industry performance since 1996. The figure shows the number of NDAs approved by CDER between 1996 and 2004. Similar graphs, usually showing the same time period, have been used by others to argue that there has been a decline in innovation rates in the pharmaceutical industry.

time of approval were thought to provide a significant clinical advantage over existing medication: priority NCE refers to FDA-approved drugs that provide a substantial advantage over existing treatments (whether or not they are 'first-in-class' for a new disease mechanism), as judged by the FDA at the time. The definition of the pharmaceutical industry includes small companies and biotechnology companies. This is deliberate, because the analysis covers a 60-year timeframe and companies that used to be small are often major firms today. In addition, the knowledge, capital and skills required to develop a new entity successfully, in most cases, need a partnership between biotechnology and big pharmaceutical companies. There is also a strong perception that innovation refers to the original idea or finding that triggers a drug discovery programme. This is not true. Bringing a drug to market could require literally hundreds of innovative steps. Every aspect, including synthesis, formulation and clinical trial design, requires innovation if a programme is to be successful. Thus, innovation (the successful launch of a new drug) is inextricably interwoven from an early stage: from interesting new academic findings or industry research providing a starting point, through lead compounds, which arise from the efforts of large and small companies, to the eventual NCE. Here, remarkable findings that directly contradict current perceptions of the industry are discussed.

Nothing is more difficult than measuring true performance in pharmaceutical R&D, because of the lag-time between the commencement of a R&D programme and a drug reaching the market. Even the best performance indicators, such as the numbers of compounds in advanced stages of development and the likely commercial and/or medical value of their indications, are limited in their ability to predict real outcomes. For this reason, NCEs approved by the FDA and/or Centre for Drug Evaluation and Research (CDER) as a more definitive outcome measure were used for the purpose of this analysis. In addition, we adhered to the FDA categorization code, which divides new medicines into 'priority' and 'standard'. However, because the FDA assesses the probable advantage of a new prospective medicine for the patient at the submission of a new drug approval (NDA), this analysis does not always correlate with the proven advantage of a new drug once it reaches the market place. Other, equally valid, categorizations, such as first-in-class medicines versus 'followers', could have been used, which would have been a measure of the intent of the industry to produce novelty and thereby provide value to patients. This method would have ignored the fact that 'best-in-class' medicines offering significant advantages often come from follower compounds. Thus, whereas neither categorization seems perfect, the FDA priority classification has been used for the purposes of the analysis discussed here. This method means that the raw data are not biased by the prejudices of the authors and are readily accessible by the reader. US-approved new vaccines and biologicals (primary indication only) were also analysed [1].

How innovative is the pharmaceutical industry today?

Between 1996 and 2003, there appears to have been a steep downward trend in FDA-approved NCEs (Figure 1). It is on the basis of this time period that many analysts consider the pharmaceutical industry as being less innovative than previously.

1996: an exceptional year for drug approvals

It is apparent from the data that 1996 was an exceptional year (Figure 2), with an uncommonly large number of NCEs approved, more than in any previous or following year. Some (www.cato.org/pubs/regulation/regv25n1/v25n1-2.pdf) have suggested that this success was the result of the FDA reform in 1992 (PDUFA). This reform introduced user fees, paid by the pharmaceutical industry, to help remove resource bottlenecks. This seemed to have accelerated review times and could have led to the earlier approval of some NCEs. If this is the case, then it is conceivable that a compression effect resulted, which artificially increased drug approvals in some following years.

Effects of QT prolongation on drug approvals

By 1998, QT prolongation emerged as a major safety issue, affecting many classes of drugs. This was precipitated by the withdrawal of terfenadine and cisapride from the US market, because of sudden deaths associated with QT interval prolongation. The subsequent focus on QT led to the re-evaluation of many drugs on the market and in development, and is likely to have contributed to the lower

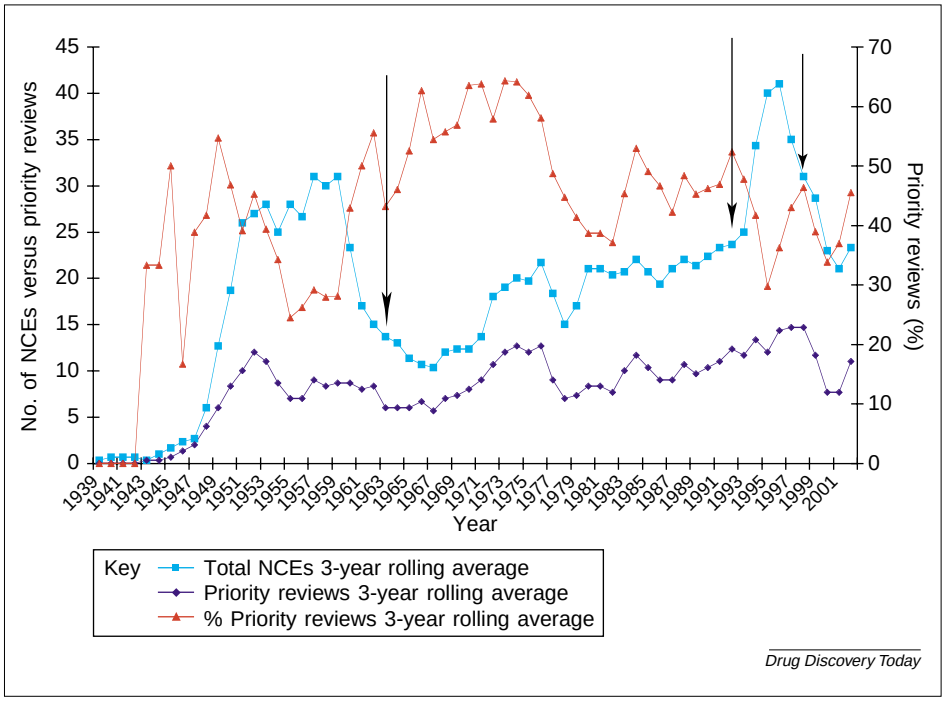

FIGURE 2

Industry performance since 1945. The first arrow indicates the Harris-Kefauver amendment coming into effect in 1963, the second arrow shows the introduction of FDA user fees in 1992 and the third arrow depicts the year 1998 when QTc interval prolongation started to be recognized as a clinical safety issue.

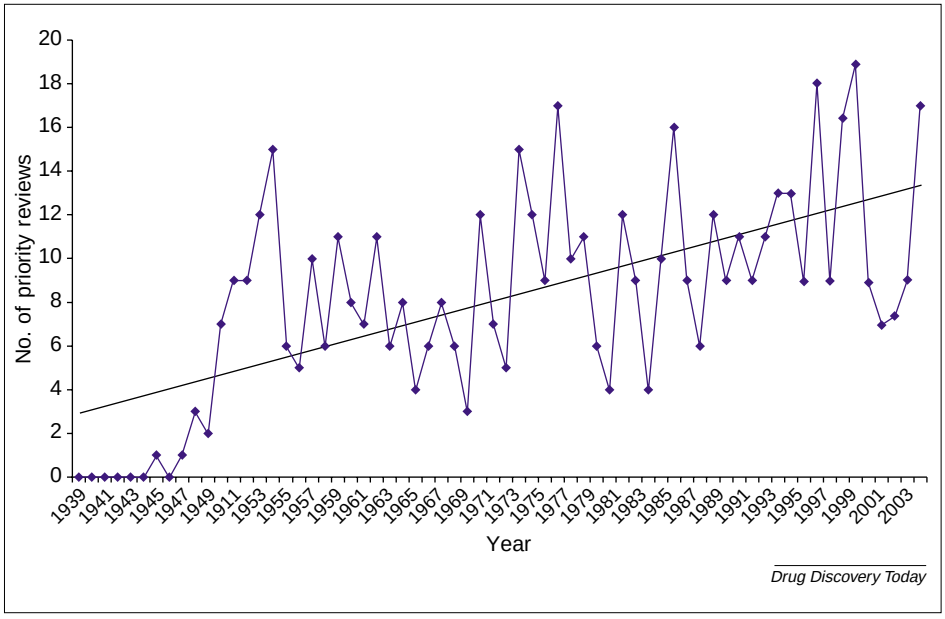

FIGURE 3

Cyclical pattern of priority reviews over time. Cyclical pattern of priority reviews over time. The black line is a trendline. The pharmaceutical industry is regularly accused of producing an increasing proportion of 'me-too' drugs, which do not show advantage over existing treatments. This figure shows data that contradict this proposal. Over the years, while there have been fluctuations, the overall trend has been one of increasing numbers of priority reviews. These are drugs that the FDA believed had the potential to provide substantial advantage over existing treatments.

NCE approval rates from 1998 onwards (Figure 2). Thus, whatever the reason for the 1996 peak, it cannot be regarded as a benchmark for pharmaceutical innovation capabilities.

Priority reviews

During 1996, despite the high total of approved drugs, there was only a relatively low percentage (just over 30%) of priority reviews (Figure 1) among them. In comparison, over the entire six decades, almost a half (46%) of all new drug introductions were priority reviews. Although we would not suggest a mathematical correlation, there appears to be a trend towards lower numbers of priority reviews in years when the total numbers of NCEs are high, and vice versa (Figure 2). Thus, between 1965 and 1994, the highest percentages of priority reviews as a function of total drug approvals can be observed – 57%, 48% and 49% in the third, fourth and fifth decades, respectively (data not shown). This could be explained by a cycle of first-in-class medicines, followed by follow-on compounds. After this, the area might offer no more scope for improvement. Further differentiation requires first-in-class medicines or substantial differentiation (e.g. subtype selectivity). Because it is often difficult to predict whether or not or how much differentiation can be achieved with either an improved follower or a novel drug class, such innovations tend to be riskier and programmes that aim to deliver them usually suffer higher failure rates than standard programmes. This is likely to result in a lower number of overall NCE approvals, leading to an anticyclical phenomenon between priority and overall NCE launches.

Despite fluctuations in the percentage of priority reviews over time, there has been a constant increase in the total numbers of priority reviews approved by the FDA. Thus, it is the current decade that produced the highest numbers; a total of 117 priority review medicines. The fifth decade produced 109 and the second, third and fourth decade yielded 78, 78 and 92 priority reviews, respectively.

For a deeper understanding of the peaks and troughs of drug approvals, the influence of the regulatory climate over time cannot be ignored. In 1963 and 1998 (Figure 2), significant changes to regulatory hurdles occurred, with subsequent, negative effects on total drug output. Despite this impact on drug approvals, the respective proportions of priority reviews within these diminished cohorts rose. Thus, although fewer drugs were approved (and/or submitted),

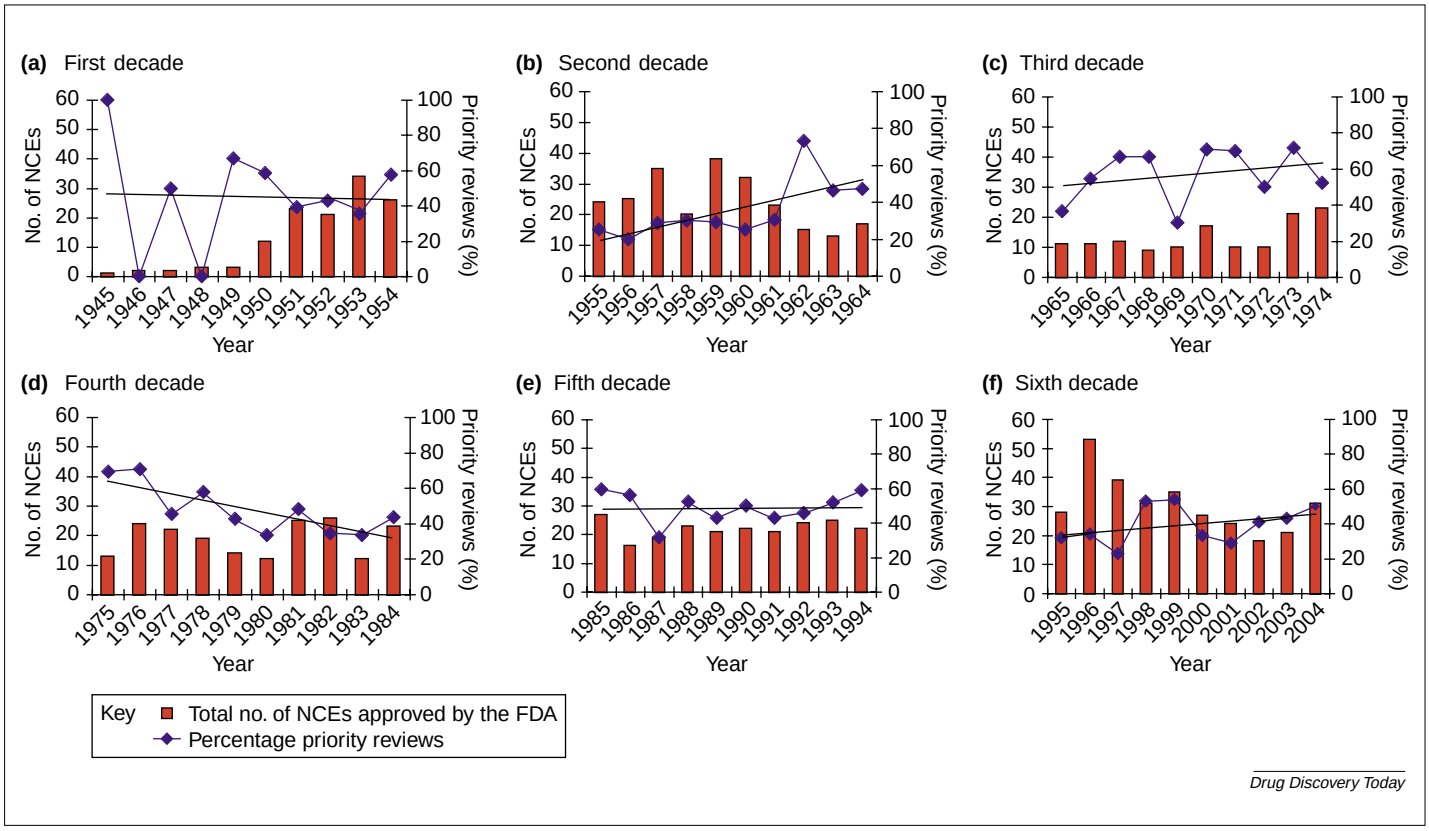

FIGURE 4

Six decades of industry performance. (a), (b), (c), (d), (e) and **(f)** each represent one decade of R&D output. The black line is a trend line of percentage priority reviews. The total numbers of NCEs produced in each decade were: (i) 127 in the first decade; (ii) 242 in the second decade; (iii) 134 in the third decade; (iv) 190 in the fourth decade; (v) 220 in the fifth decade; and (vi) 307 in the sixth decade.

those that cleared the regulatory hurdles were medicines from which significant disease treatment advantages were expected.

Over a longer timeframe, priority reviewed NCE approvals (Figure 3) and total NCE approvals (Figure 4) rose steadily. Total approvals reached a record high of 307 entities between 1995 and 2004. Had vaccines and those biologicals that are not approved through CDER been included, this figure would rise to 381 (Figure 5). Thus, it would appear that the 1996 'peak' and myopic focus on near-term performance has set a myth in motion, which bears no relationship to the true innovation rates of the pharmaceutical industry. Time course analyses, such as ours, are not only important as reality checks, they might also be able to shed light on practices, good or bad, that affect performance. For example, what led to the high performance observed in the second decade (Figure 4)? What caused the drastic reduction in drug approvals in the third decade? Why was the return on the drugs produced in the fourth and fifth decades sufficient to lead to a comfortable period of growth? Why would the current decade have such impressive innovation rates and yet leave the pharmaceutical industry fighting for survival? An answer to these questions might lie in the events that occurred during these time periods, as well as in changing R&D practices.

What are the distinguishing factors in each of the six decades?

The post-war growth era

The first ten years (Figure 4) after World War II were a period of growth, during which the US pharmaceutical industry came to dominate medicinal R&D globally. This was, in part, because of the military need for modern medicines during the war. The investments made in essential wartime goods also benefited other industries, for example, aeroplane manufacturers. Pharmaceutical and aeroplane manufacturers then made the successful post-war transition to market economics in the USA. It is noticeable that the aeroplane manufacturing industry has analogous cycles of consolidation among major manufacturers (McDonnell and Douglas amalgamating to form McDonnell Douglas Corporation, Rockwell merging with Boeing and finally McDonnell Douglas Corporation joining with Boeing; a similar cycle happened in Europe, creating Airbus). This consolidation was accompanied by the constant formation of small aviation companies supplying niche markets (e.g. Velocity, Moller and Sino Swearingen), paralleling the biotechnology birth of new small pharmaceutical companies. In direct contrast to the pharmaceutical industry, the number of major plane launches has declined and yet lack of innovation is not a charge that is levelled at this industry.

Early post-war, breakthrough discoveries by the pharmaceutical industry, such as cortisone, were highly significant in health care. This growth continued into the second post-war decade, when the industry managed to build on some earlier discoveries (such as steroid chemistry) fuelled by increasing R&D investment. As a result, the second decade showed almost double the output of new medicines compared with the first decade, but also a low proportion of priority reviews. Despite this slowdown in more substantial, differentiated innovations, some important novel, first-in-class medicines were discovered in the second decade, such as tolbutamide (Glucotrol) for type II diabetes and chlorothiazide (Diuril), the first diuretic. However, the end of the second post-war decade heralded the beginning of the thalidomide crisis. As a consequence, the Harris-Kefauver Amendment came into force in 1963, which led to increased focus on safety and efficacy of new drugs. The additional testing requirements had consequences for NDAs (Figure 4): only 134 new drugs were approved.

The impact of new regulations on drug approvals

As a result of these new regulatory hurdles (which almost certainly would have seen drug approvals granted to drugs the FDA considered as most likely to provide substantial advantages over existing treatments), the third decade produced a significant proportion of priority reviews. However, can information from this period teach us how to do R&D on a lower cost base (Figure 6) while producing ever more NCEs? The first three decades might not easily lend themselves to identifying successful practices that could impact the processes of today. There have been substantial changes in the understanding of drug quality (in terms of safety, efficacy and differentiation) by pharmaceutical companies and by regulators, which, incidentally, is one reason why the cost base of the pharmaceutical industry is rising exponentially (Figure 6). Nevertheless, some practices have been retained by the drug industry throughout the decades, such as the use of breakthrough discoveries as a base from which incremental improvements can be produced. Furthermore, relevant tissue and animal models were in routine use, which have helped in the discovery of receptor subtypes and the elucidation of their physiological function. This also is a practice that the pharmaceutical industry has started to re-appreciate in today's human genomics and recombinant protein target-led R&D environment. Finally, the close relationship between academia, research institutes and pharmaceutical companies has been instrumental in driving the understanding of pharmacology. This has led to many new areas of the science as a direct result of studying the pharmacology of the ever-increasing panel of available, efficacious drugs and their analogues. The growing numbers of selective drugs for various α- and β-adrenoceptors, and their ability to impact alternative therapeutic indications, is a case in point (Figure 7). Ironically, it is this drive to understand the full utility of existing drugs that now earns the industry much criticism, because what are seen simply as patent extension strategies are actually highly valuable new applications for existing drugs. For instance, sildenafil, the breakthrough therapy for male erectile dysfunction marketed as Viagra, has been recently submitted as a treatment for pulmonary hypertension under the tradename Revatio.

It is noteworthy that the climate after the thalidomide crisis suggested the demise of the entire pharmaceutical industry. Despite this, the industry recovered to experience a golden era (in financial terms) in the 1980s and early 1990s.

In spite of the negative forces impacting the industry in the 1960s, important drugs such as haloperidol (Haldol) for psychosis, indomethacin (Indocin), a non-steroidal anti-inflammatory drug, levodopa (Sinemet) for Parkinson's disease, ethynil estradiol (Estinyl), an improved contraceptive, and many others, were brought to market during the period from 1965 to 1974. These drugs provided the foundations for important improved drugs, which were crucial for the recovery evident in the fourth, fifth and sixth decades. Thus, these time periods might be most useful for the provision of insight into R&D innovation.

The impact of new science and technology developments on drug approvals

An increasing proportion of new drugs were discovered via novel science, such as the angiotensin-converting enzyme (ACE) inhibitors. At the beginning of the 1970s, ACE inhibitors were rationally designed from starting templates that were polypeptide inhibitors [2]. In the 1980s, molecular biology started to become a more integral part of R&D, although it was only recently that the first molecular biology-based small molecules (such as Gleevec) reached the market, illustrating the long cycle

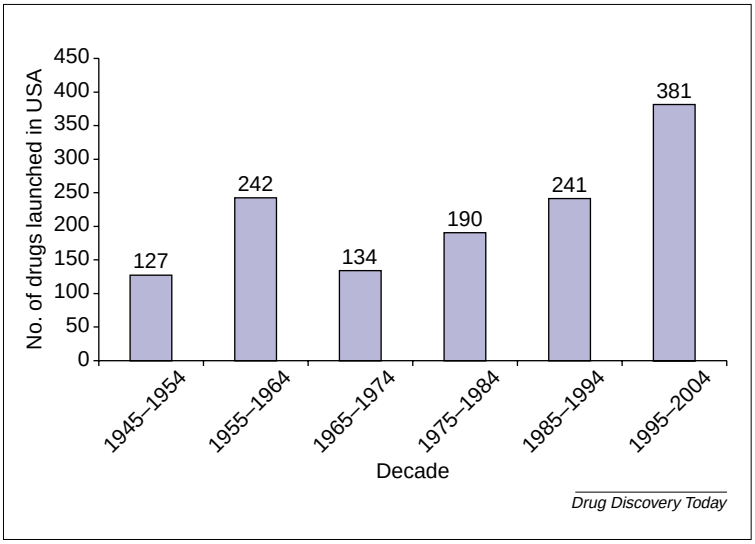

FIGURE 5

Total number of drug launches in the USA. The total number of drugs launched includes biologicals and vaccines: in the past two decades, approvals of biologicals and vaccines have increased and this has added to the rising number of CDER-approved NCEs (compare with Figure 4).

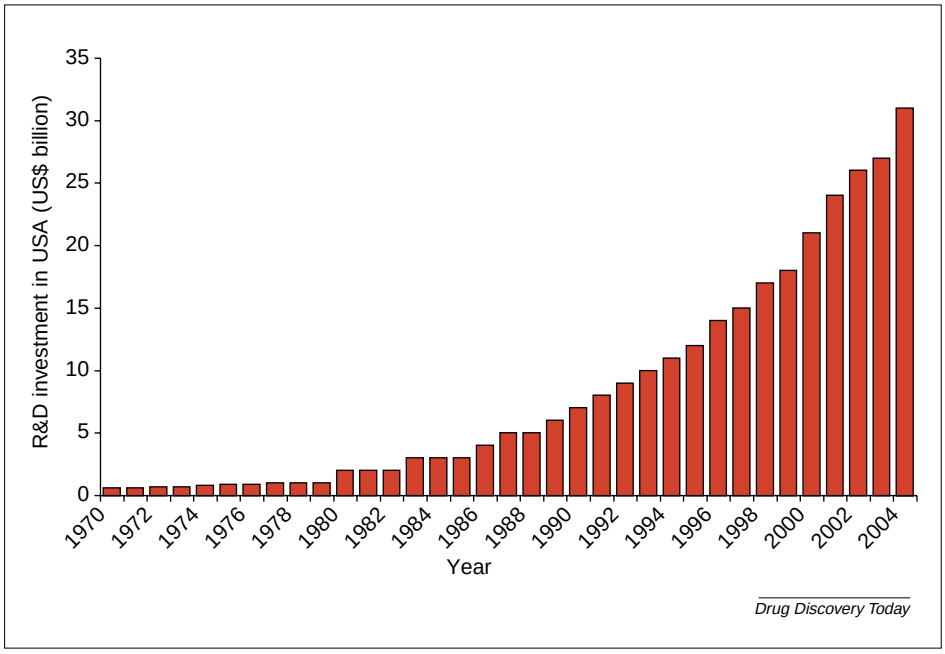

FIGURE 6

R&D investment in the USA between 1970 and 2004. Source is the PhRMA annual survey (www.phrma.org/publications/publications/17.03.2005.1142.cfm).

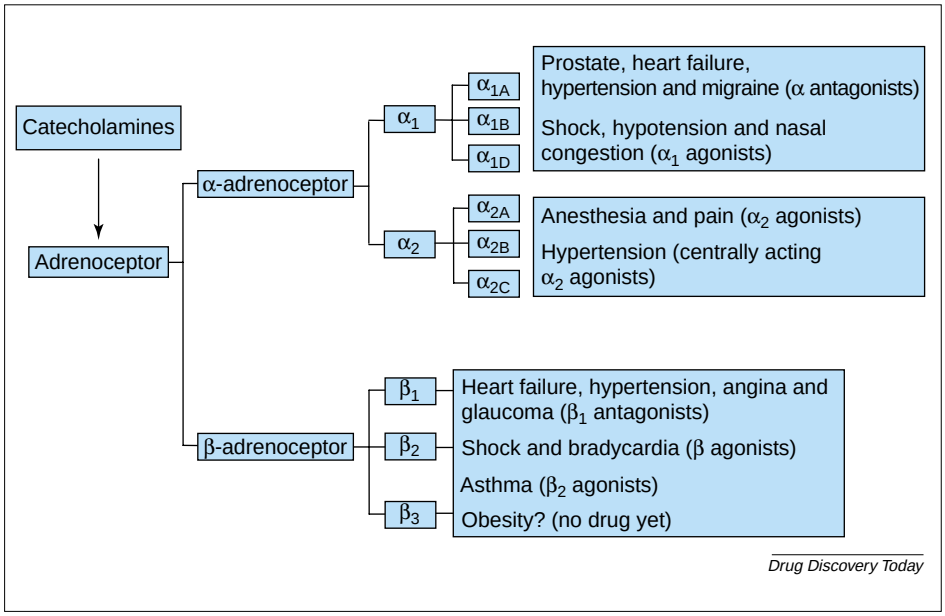

FIGURE 7

Receptor subtype discovery and the effect on widening impact on new diseases. The discovery of the effects of catecholamines on adrenoceptors was the first step in a long journey of discoveries. Analogues and chemical derivatives of catecholamines provided the initial tools to identify a host of adrenoceptor subtypes and explore their pharmacological function. This, in turn, opened up new indications and drug discovery efforts to provide selective medicines for these new disease areas, as well as a growing arsenal of selective agonists and antagonists with which to further explore the pharmacology of these receptors.

time required for drug development. Of course, some biotechnology companies managed to exploit the promise of the new biology advances much earlier, through an intense focus on these new biological technologies, and they have contributed to a steadily growing biological product introduction between 1985 and 2004. Thus, the more recent years distinguish themselves through a much more technology driven R&D process (which has also contributed to the exponential rise in R&D investment). Contrary to popular belief, these R&D investments, at least in part, have led to more drug introductions (or at least not hindered them).

The fourth and fifth decades are unique in that they represent the beginning of the blockbuster phenomenon. This meant that for an exponentially growing R&D investment a return on investment was achieved that was not only dependent on the numbers of NCEs launched but also on the commercial value of each NCE. This, in turn, provided an environment, in which more R&D investment was feasible and necessary (Figure 6), to produce the next wave of blockbusters. One of the reasons that the drug industry is today perceived as being in trouble is the extraordinary success of this blockbuster paradigm. With single drugs achieving in excess of US$1 billion in sales, and the long cycle times in R&D, companies needed to have discovered the next more successful drug and have it in early development to replace the earnings of its newly marketed predecessor. Without an exponential increase in drug approvals far outstripping past performance, new financial models will be needed. However, we assert that the innovation capabilities of the drug industry are not to blame for the current dilemma and that other solutions must be found, outside the standard plea to drug discoverers to increase their levels of innovation. The real issues lie in the cost base of the industry – it has simply become highly, or even too, expensive to produce a new medicine. Therein lies the problem for which solutions should be sought by pharmaceutical companies and regulators.

During the fourth decade (1975–1984), companies were able to build on some breakthrough discoveries from the previous period, as well as introduce the next wave of new first-in-class drugs. This produced some interesting drugs, such as clotrimazole (Canesten), a popular topical antifungal and first azole antifungal drug. Canesten was followed by several oral azole drugs, including a 'blockbuster' improvement, fluconazole (Diflucan), an important oral antifungal drug approved in 1990. Other drugs launched between 1975 and 1984 included prazosin (Minipress), the first α-adrenoceptor antagonist for hypertension, and cimetidine (Tagamet), the first histamine H_2 receptor antagonist for gastric ulcers.

Many of these drugs were the beginning of an improvement wave, which gave rise to blockbuster drugs between 1985 and 1994. During this timeframe, 109 (almost 50%) priority reviews, some of which were first-in-class drugs and others that were followers, were deemed to provide substantial improvements. In addition, this period produced some highly commercially valuable drugs, such as amlodipine (Norvasc), a calcium ion channel blocker for hypertension, or fluoxetine (Prozac) for depression. The start of the current decade also saw some remarkable blockbusters, such as atorvastatin (Lipitor), which, so far, has produced the highest revenues ever seen in pharmaceutical history. Whether or not there is a reduction in the numbers of blockbusters in the middle of the sixth decade is a current debate. Many of the novel mechanisms appear to target indications with smaller patient numbers (niche markets), albeit of a significant medical need, such as cancer, which would suggest lower commercial value. However, the blockbuster status of drugs such as Erythropoietin (Epogen) indicates that such conclusions might not be totally accurate. Between 1995 and 2004, the total numbers of NCEs (307) and the total number of priority reviews (121) were the highest observed since 1945. Although there was clearly a downturn between 1996 and 2004, the past three years are showing rising trends again. Such short-term fluctuations are not unusual (Figure 2).

More significantly, many priority reviews occurred in high medical need areas such as cancer, exemplified by the launch of imatinib (Gleevec). There is a period of time when expanding scientific knowledge base and new technologies provide quantum leaps in output. The past decade has witnessed this in the field of oncology. Despite the significant scientific challenges associated with understanding the different molecular mechanisms underlying different tumour phenotypes, huge progress continues to be made. In particular, innovation rates in oncology have rapidly increased (and are projected to increase in the future) in recent years (www.accessdata.fda.gov/scripts/cder/onctools/druglist.cfm), thanks to advances in molecular biology and a supportive regulatory authority (Figures 8,9). The advances in molecular biology have increased the understanding of tumour mechanisms (to produce targeted small molecule drugs) and the industry's ability to produce recombinant therapies (antibodies and palliative biological treatments, for example, Erythropoietin).

The real issues affecting R&D today

So why would the most productive decade (in absolute terms and in terms of numbers of priority reviews, many of which are addressing high medical need) – the sixth – be associated with so much negativism, industry consolidation and reduction in profit growth? The answer does not lie in the output or the innovative capabilities of the industry, which have been rising throughout the history of the industry. Rather, it seems multi-factorial – price pressures, record levels of US pharmaceutical R&D investment (Figure 6), increased competition, market fragmentation and generic erosion all appear as contributing external factors that reduce margins.

Furthermore, despite this increase in innovation, the issue of high R&D costs has not yet been adequately addressed. In relation to financial investment, the second decade was remarkably more productive in financial terms, although not in absolute terms. By contrast, the past ten years have produced the highest number of new entities, but at the same time it now costs the pharmaceutical industry almost US$1 billion (http://csdd.tufts.edu) to bring one such NCE to market. This is partly because of the need for technology investments, higher regulatory and commercial hurdles and associated higher failure rates, and also increased costs of large clinical studies to meet regulatory and commercial requirements. Over a ten-year period, the number of patients enrolled in clinical studies alone has increased by 135% [3]. It is plausible that, in addition to regulatory and commercial requirements, the increasing proportions of priority NCEs might have contributed to these spiralling costs. The higher risk associated with such priority reviews means that many of the programmes dedicated to discovering and developing such differentiated innovations will have failed before reaching the market, thereby contributing substantially to R&D costs: this phenomenon is perhaps best exemplified by Figure 2, which shows an inverse relationship between the total numbers of new drugs brought to market and the proportion of priority reviews. The higher the percentage of priority reviews, the lower the total number of new medicines. This means that the economic aspects of R&D costs, particularly those associated with priority reviews versus the revenues achieved by the drugs launched in the previous approval period, have yet to be solved. Today, there is a widening gap between investment and return, which cannot be solved by 'increasing output', given that output has been increasing over three consecutive decades. Unless policy makers and prescribers truly value innovative new drugs, based on the risks and costs it takes to produce them, there is little hope that this widening gap can be closed with strategies other than continued mergers and significant reduction of R&D investment. The probable effect of a reduction in investment in R&D on the future ability of the industry to produce much-needed substantial, differentiated innovations in high medical need areas, such as cancer, where the science has just ripened to facilitate targeted approaches, is left to the imagination. This somewhat pessimistic assessment of the future economics of the drug industry, because of external influences, does not mean that R&D can rest on its laurels. Managing innovation is as important today as it was during the past three decades. However, today, there is a supplementary ingredient that must be added – to make wise choices and thus reduce attrition, so that costs can be reduced as part of the innovation process.

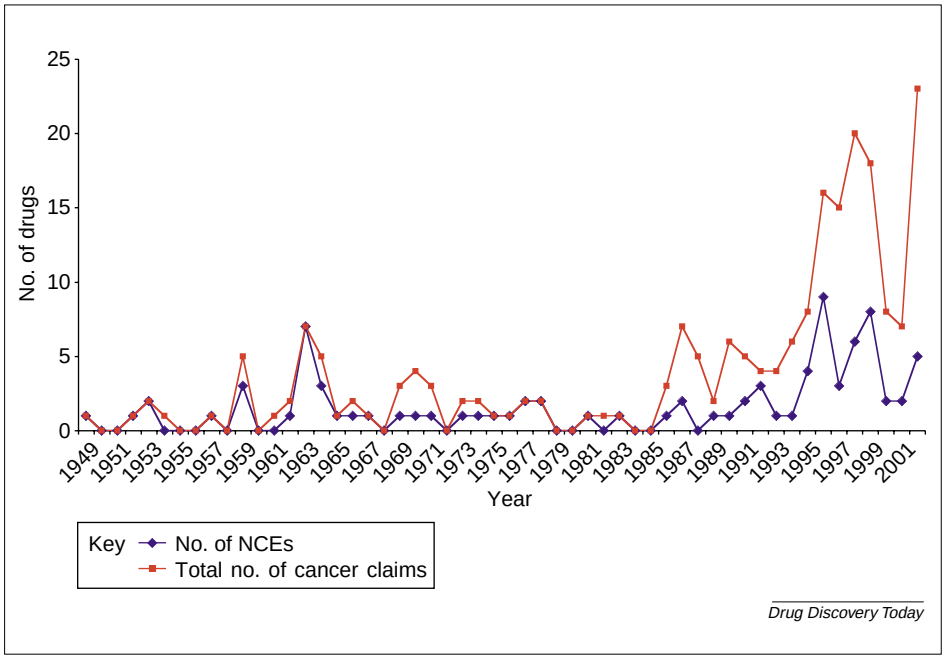

FIGURE 8

Annual oncology drug approvals. The total number of approvals includes existing cancer drugs for new cancer indications.

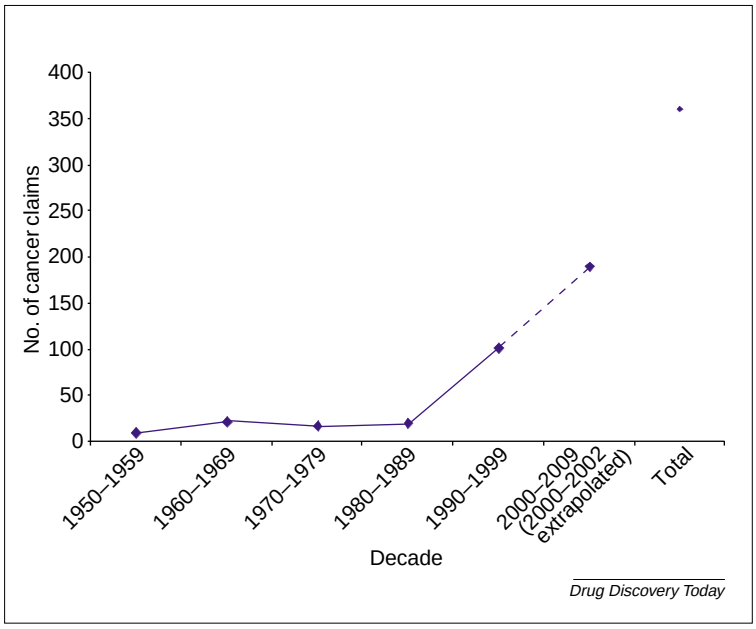

FIGURE 9

Oncology drug approval by decade. This represents all new approvals, including existing oncology drugs for new oncology indications. Projected trends for the coming decade are also included.

Innovation, cost and benefit:risk perceptions

Even in growth areas, such as biologicals, where the outcome at the start of R&D seems more predictable and where the success rate to market appears much higher, the costs of production and the need for parenteral delivery often offset the gains in R&D output. Not only can this restrict the commercial potential (although there are remarkable exceptions, such as Epogen and Enbrel), it also limits availability to patients because only subsets of patients, where lack of alternative therapies justify the additional costs, will benefit from these discoveries. There is no doubt that cost (and reimbursement issues) is one limiting factor that prevents the transformation of R&D projects into innovative new products. In addition, the industry's successful history has led to the availability of many effective, safe medicines in areas of high medical need. Some of these drugs are already generic or will turn generic over the next decade. This means that today the hurdle for innovation has become much higher. There is still significant unmet medical need in almost all diseases afflicting mankind, but the requirements regarding safety, efficacy and convenience are constantly increasing. Even in life-threatening diseases, such as HIV, there is now an expectation that chronic therapy be as tolerable and convenient as possible, to ensure compliance (and thereby efficacy).

Benefit:risk is an almost impossible ratio to quantify across the spectrum of medicine in an area so clouded by emotion and changing societal values. It is impossible to produce anything that is completely safe in any walk of life. Depending on perspective, the value placed by society on particular issues varies and is hugely influenced by changes in social and political climate. The fundamental problem is that no matter how much data are collected to demonstrate that a drug might be safe, it is always possible that the next piece of data might be contradictory. Because it is difficult to detect adverse events of a drug affecting a few individuals (as a result of the natural background incidence of many of the side effects associated with drugs), the timescales are lengthened to show that the drug is unsafe. The overall effect can be hugely damaging to the public's view of benefit:risk, because patients will have been prescribed the drug following the initial observation of 'safe' and continued until the data enabled the conclusion that the drug is 'unsafe'. This is compounded by a media that tends to sensationalize headlines, when the findings are often preliminary or only suggest a possible association. Another commonly cited analysis is the high number of hospital admissions (e.g. 6.5%) as a result of adverse drug reactions [4]. This suggests, and is frequently phrased to imply, that drugs do more harm than good and that, compared with old 'safe' medicines, new therapies are of high risk. Inspection of the data [4] indicates the need for new drugs. Warfarin, furosemide, bendroflumethiazide and aspirin account for 46% of hospital admissions for adverse drug reactions in hospitals in Merseyside (UK) [4]. Aspirin used alone, or in combination with other drugs, is associated with 61% of the deaths in this study as the result of adverse drug reactions. It is

unlikely that this perception of risk is generally shared throughout the population. The logical societal response, in the belief that new drugs must be less safe than old drugs, is to demand tighter regulations on new drugs. This can help to suppress innovation to a point, where those most in need of novel or improved drugs might no longer be able to obtain them. There is already a precedent for this scenario. Despite the major beneficial impact vaccines have had on society at large, virtually eradicating infant mortality from infectious diseases in industrialized countries, the same companies have been forced out of business by regulation and diminished profit margins. Today, so few manufacturers remain that, for example, a minor production problem could have wiped out a half of the influenza vaccine supply for the USA for 2004. Nowadays, the demands of society with respect to safety cannot be assured through clinical trial populations alone. For example, in the UK, Bextra was withdrawn for two serious adverse events out of 40,000 patients: this could only be discovered after launch.

Conclusion

The concept of innovation today is different to the concept of innovation 20 years ago. Yet, if measured by NDAs, scientists today are as innovative, if not more so, than 20 years ago. The myth of the innovation deficit is exactly that – a myth. Scientists today have to walk a tightrope of forces that work against innovation and make R&D much more expensive. Never before did scientists have to consider the market, safety and commercial aspects so early in R&D as they must today, in addition to finding ever more-effective drugs for increasingly well-served, but still needy, markets. In refocusing on high medical need areas and bringing priority agents to patients, the drug industry is experiencing the financial impact of attrition and niche markets. The increase in costs through higher attrition and increased regulatory demands, as well as the phasing out of the blockbuster business model, but certainly not a decline in pharmaceutical innovation, are the true reasons for the current woes of the industry. Perhaps those that criticize the pharmaceutical industry should recognize that the industry's continuing track record of innovation, to alleviate human suffering, is the basis for optimism for the future.

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