# Managing innovation in the pharmaceutical industry

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## Abstract

Innovation is the lifeblood of the pharmaceutical industry, and has been a major driver of industry growth, as well as providing major advances for patients and society at large during the last century. Despite this record of success, the industry is currently under attack for its perceived lack of innovation. In this paper, data are provided that demonstrate that the pharmaceutical industry today is more innovative than even in its rapid, postwar growth period. The authors discuss in depth a framework for how today's R&D organisations can continue to be innovative.

***Keywords:*** *innovation, management, pharmaceutical industry*

## INTRODUCTION

Since 1996, the output of the pharmaceutical industry has been declining. This has led many internal and external stakeholders to question the innovation capabilities of the industry or of the industry's scientists.[1–3] In this paper, a time course analysis is given, which puts this phenomenon into perspective, and also the process that might help internal innovation to flourish is discussed. Food and Drug Administration (FDA) legacy data and categorisation codes are used to identify the total numbers of non-chemical entities (NCEs) approved, as well as the number of priority-reviewed drugs, which are termed radical innovations.

## INNOVATION TRENDS

Between 1945 and 2004, despite an underlying cyclical performance, an overall upward trend can be readily discerned when plotting drug approvals by 10 year intervals (Figure 1).[4] What is more, the approval rate of priority drugs has also gone up over the decades (Figures 2 and 3). This is in direct contradiction of current opinion that the industry is no longer innovative. There are two reasons why this analysis was included in our discussion about managing innovation: firstly, to look back to the most innovative period and try to glean best practices for today; and second, to give the readers a deeper, data-driven, perspective on the pharmaceutical industry's true innovation capabilities, and decouple them from popular, commercially driven views.

The results of our analysis were surprising, and have led us to the conclusion that the current decade is the one to focus on for best practices in managing innovation. These data are also challenging the popular view that big pharmaceutical companies are less innovative than the biotechnology industry. When considering the companies that registered the medicines discussed in this paper, the vast majority turned out to be big pharmaceutical companies. While undoubtedly a certain percentage of these drugs will have originated from biotechnology, there is little evidence that biotechnology on its own managed to bring substantial numbers of small molecules to registration and approval. Rather, the partnership of both industry sectors seems to have led to the increase in small molecule drug approvals over the past two decades (Figure 1). A further boost that increased the total numbers of medicines (Figure 4) brought to patients has come from vaccines and biologicals – here biotechnology has had a major hand in providing novel therapies,

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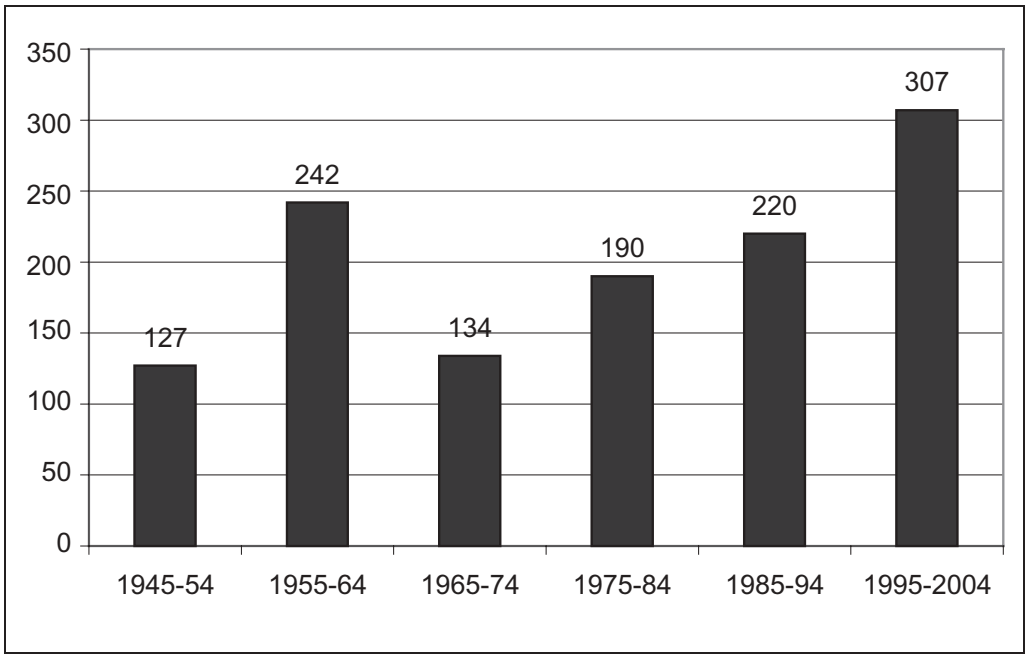


**Figure 1:** Pharmaceutical industry contribution to total drug approvals by the FDA (CDER) in each of the six decades

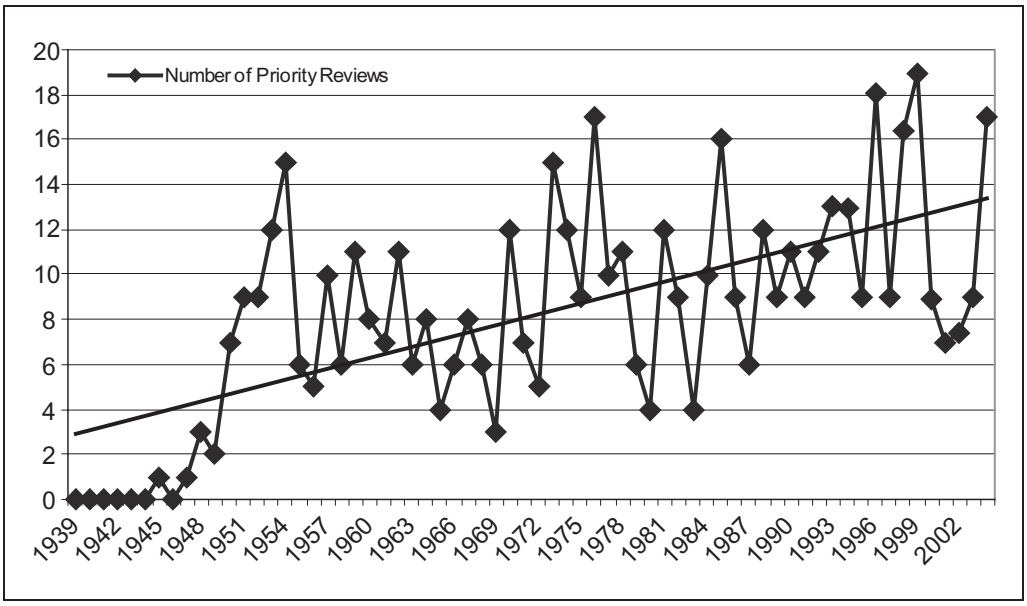


**Figure 2:** Cyclical pattern of radical innovations over time: the absolute numbers of new priority reviewed approvals each year by the FDA. The straight line is the trendline

**High throughput screening is beginning to positively affect innovation**

especially into high medical need areas, such as cancer.

## THE CURRENT DECADE

The data speak for themselves; over the past 10 years both the biotechnology and the pharmaceutical sectors have produced significantly increased numbers of new medicines, a substantial proportion of which the FDA deemed as providing potentially significant advantage and classified them for priority review. So what is different today that made these innovations happen at such higher rates? And why is the mood so negative regarding the pharmaceutical industry's innovation capabilities?

### Drivers for innovation today

There have been major advances in the biological sciences over the past 20 years. In the 1980s, molecular biology was

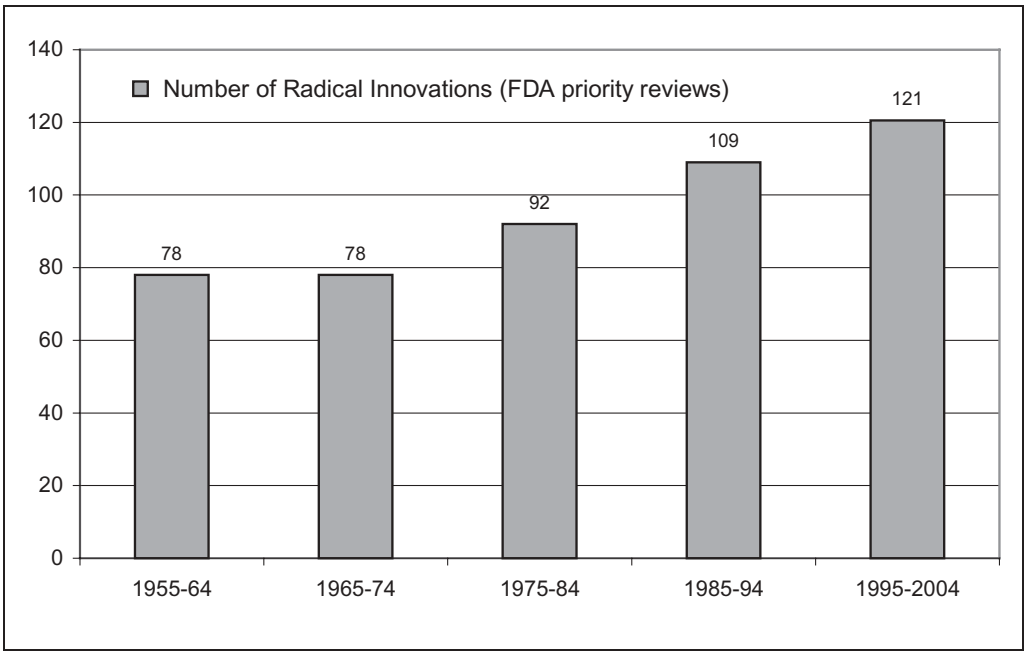


**Figure 3:** Pharmaceutical industry contribution to priority-reviewed drug approvals by the FDA over the past five decades

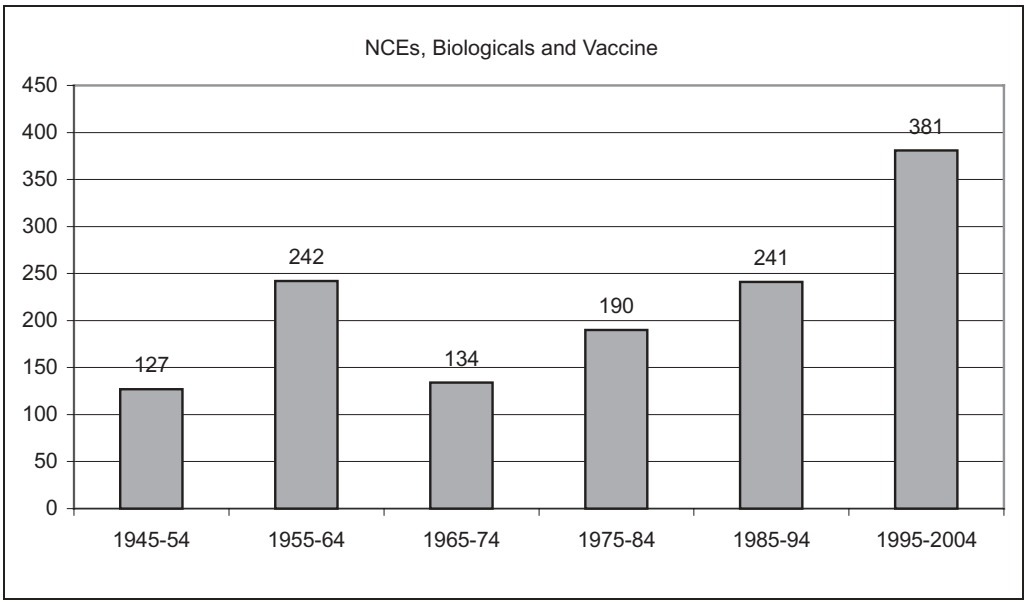


**Figure 4:** Pharmaceutical industry *and* biotechnology contributions to total drug approvals by the FDA in each of the six decades. Significant additional drug launches in the last two decades are due to biologicals

**Innovation is on the increase**

introduced into pharmaceutical R&D, even though it took until the 1990s for the first molecular biology-based small molecules (such as Gleevec) to be approved.[5] Major pharmaceutical companies also invested heavily in high-throughput screening (HTS) by the mid-1990s. Although some successes (such as Gleevec, which derived from subset screening) may be attributable to this investment, the large majority of drugs produced so far have not been discovered using HTS. That is not to say that future drugs may not originate from this technology: Pfizer's own UK-427,857, a promising, novel CCR5 receptor antagonist[6] for the treatment of HIV/AIDs, is HTS-derived, and well advanced in full development.

Judging by the Phase III population in

**R&D costs have become crucial for the pharmaceutical industry**

databases such as IDDB, it would appear that many more companies are in the process of bringing medicines to market that have either been identified via HTS screening, or have derived from today's understanding of pathway biology. Thus, the reductionist paradigm (molecular target-based drug discovery), which has been much slated in recent times, is starting to compare more favourably with the old, holistic paradigm (tissue and animal-based drug discovery), which has produced most medicines so far.

One of the major drivers of innovation may also have been a much greater fiscal focus of the major pharmaceutical companies. The patent expirations of major blockbuster drugs, such as Prozac and Zantac, exemplify the dilemma of the entire pharmaceutical industry – for each expiring major blockbuster drug, normally more than one new medicine has to be brought to market in order not only to replace revenues, but also to continue to grow them. This has led most pharmaceutical companies to tighten up internal management procedures, benchmark their R&D performance within the industry, and look for best practices and ways to further innovation while reducing costs. In part, this new performance- and goal-based R&D management may have contributed to increased drug approvals.

The biotechnology industry managed to exploit the promise of the new biology advances much earlier than the pharmaceutical industry, through an intense focus on new biological technologies, and has been steadily growing its product introduction between 1985 and 2004. Thus in the current decade we can observe a more technology-driven R&D process. These R&D investments, at least in part, have led to more drug introductions in the last decade.

## Negative perceptions of R&D innovation capabilities

One of the reasons why the drug industry's innovation capabilities today are perceived so negatively could be the ongoing erosion of the blockbuster paradigm. Investors and analysts do not distinguish between total drug approvals and revenues. There is no doubt that revenues are growing slower for most companies than the double-digit figures that the financial markets would like to see (even though overall the drug industry's revenues are still growing compared with other industries, which are facing stagnating or declining

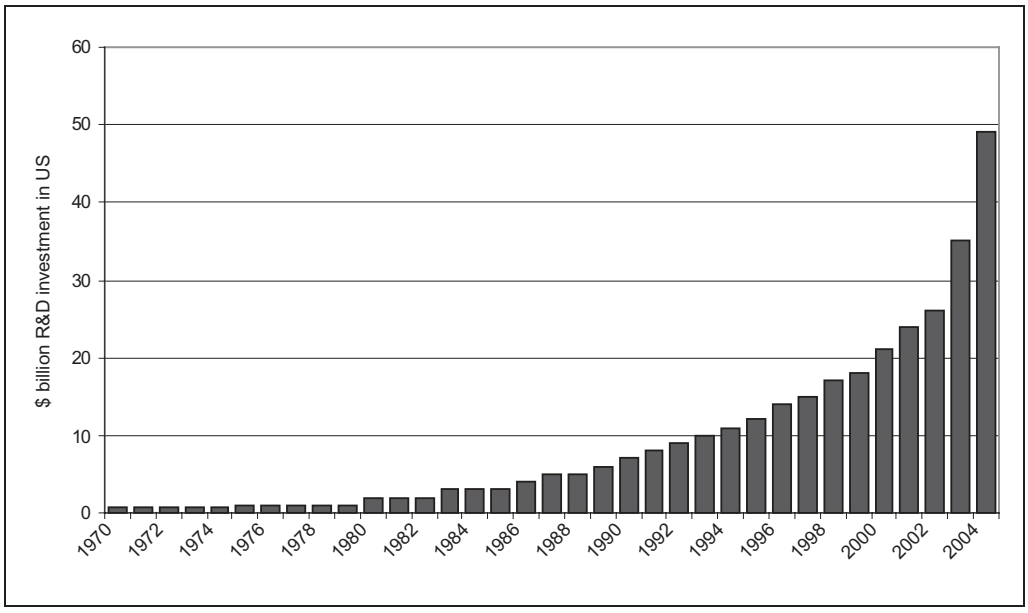


**Figure 5:** US Pharmaceutical Industry R&D investment between 1970 and 2004 Source: PhRMA annual surveys

revenues). In addition, the costs of R&D are rising exponentially (Figure 5). This means that today's innovation management needs to focus on costs as much as on output. Our paper attempts to blend in these new financial realities into how R&D might best be managed to continue to increase the numbers of new innovations stemming from R&D laboratories.

**Scientists have to consider commercial implications of project decisions**

## INNOVATION AND COST

Even for biologicals, which have a higher success rate to market than small molecules, the cost of goods and the cost of development, are often prohibitive and limit commercial potential, especially in low medical need markets. Thus, costs *v.* projected revenue limit R&D scientists in their ability to pursue new drug targets of interest. This, and the increased competition with cheap generic copies, is a major hurdle to innovation. Thus, the requirements to demonstrate superior safety, efficacy and/or convenience are constantly increasing and are a prime cause for project failure, often at a late stage in the R&D process.

**Drug discovery is becoming increasingly complex**

Therefore, innovation today is much more demanding than in former decades. Never before did scientists have to consider commercial and economic aspects so early in R&D. Yet, although this demands generalists with a broad perspective, the reality today is that most scientists have to specialise, driven by the phenomenal and rapid advances in the natural sciences over recent years. In order to turn pure creativity into a useful innovation, somehow these broader perspectives have to be built into the R&D process. This includes expecting scientists to find new ways of reducing the cost of making medicines available to broad patient populations, to differentiate over existing, available treatments and, most importantly, to demonstrate this advantage really exists. As if these hurdles are not enough, we now also experience the conundrum of having too much information and too many drug targets available, while sorely lacking those targets, where the connections to human disease have been demonstrated without doubt. In addition, hypotheses have been generated that indicate the number of drug targets amenable to small molecule intervention, which are associated or likely to be associated with human disease, is quite limited.[7] Only a limited number of extracellular targets linked to human disease are amenable to biological intervention. Although there is no risk of this 'substrate' for the industry running out in the foreseeable future, it does drive very different innovation strategies to what an unlimited universe of drug mechanisms would have driven.

For the purpose of this paper, let us assume the hurdles described above are true: cost reduction as a requirement, differentiation over effective treatment options a must in many diseases, plus a wealth of data obscuring the limited numbers of sensible drug targets available.

## POTENTIAL SOLUTIONS

The kind of problem-solving that could find solutions to the above-described hurdles broadly fall into two categories: planning and intuition. While recognising the transformational power of the latter, this paper will focus on the former, by outlining some ideas for channelling creativity via risk management and planning.

### Scientific analysis to reduce bias

Dominant mindsets play an important role in what kind of artificial boundaries we set ourselves when we seek out and then filter new ideas and projects in order to decide on which are worthy of investment. Each pharmaceutical company probably has deeply held internal beliefs (and myths) about success factors, risk factors and other criteria based on past experiences. Some of these help avoid disaster; others may pose artificial boundaries, limiting scientists' ability to move creative ideas forward in certain areas. Therefore, separating myth from reality is of great importance, even

**Decision criteria in drug discovery are only incompletely understood**

though most likely only partially achievable owing to the many missing pieces in our understanding of the mechanisms of disease, toxicity and drug disposition.

Understanding why drugs succeed and why they fail is a first step in this separation process. In fact, drug companies really can analyse only failure with any statistical power, success being relatively rare. Fortunately, there is much openness within the pharmaceutical industry, in sharing data and new insights, plus the vast network of academic and government institutions also constantly add to the pool of knowledge about, for example, structural determinants and mechanisms of toxicity, or targets involved in drug disposition and elimination and so on. In addition, in-house studies of the fate of chemicals have been of great value in our understanding of reasons for success and failure of compounds.

## Stage gates for managing risk

The collective knowledge derived from such retro- and prospective scientific analyses form the starting point for channelling creative endeavours towards more successful outcomes. A key tool in this process is the use of stage gates. These are project go/no go decision criteria, set up at various points in the R&D cycle. The criteria used for stage gates need to be derived from the collective (and ongoing) learning about success and risk factors for drug research and development, in-house data on R&D outcomes, as well as from regulatory requirements (which in turn tend to be informed by learning about risk factors). For effective risk management, the first stage gate should be placed at project initiation, so that new ideas can be filtered. Such an early stage gate would be more concerned with strategic requirements, such as commercial aspects, the likelihood not only to develop an advantage over existing treatments, but also of being able to *demonstrate* such an advantage early. The increase in specialisation and the prospective nature of, for example, the market and competitor analysis make cross-functional evaluation of project ideas a necessity. Thus, stage gates can also be a powerful communication vehicle for interdisciplinary exchange and teamwork. They help sift the large numbers of potential drug targets into more manageable subsets.

**Effective risk management requires stage gates**

Subsequent stage gates in the discovery stage need to gradually become more specific, data-driven and stringent. The achievement of certain criteria needs to be demonstrated. The challenge for the creative scientist is not to try his or her best to avoid failing stage gate criteria. Instead the criteria should be used at the earliest possibility to pressure-test ideas by designing key experiments that would increase or decrease confidence in the scientific or strategic value of a project. Stage gates at a very early point in research can adequately represent the hurdles for innovation, outlined above, including costs. This moves the attrition 'funnel' to a point in R&D where costs are relatively low, and remedial actions can be taken very quickly. For example, if the target fails the stage gate, a new target can be sought quickly. If the compound fails, new structures can be synthesised or sought via HTS. Even more importantly, stage gates can channel creativity into finding new ways of enabling targets and molecules, for example through collaborative development of predictive models and biomarkers, much more directed use of technologies to answer questions posed by stage gates and so on.

## Downsides of using stage gates

Stage gate-based risk management needs to come with a health warning. In all process-driven planning there is a risk that what does not fit into the box gets ignored. The pharmaceutical industry cannot afford to ignore the more unusual ideas, provided they make sense, given the rapid change in its environment. There are many examples in other industries, where perhaps obvious ideas that, however, did not fit the dominant

**R&D must become more efficient**

paradigm, were ignored at great cost. Scientists that 'grew up' in a small-molecule R&D paradigm may not find it easy to dream up entirely new ways of meeting patient needs. Nor would stage gates encourage a fair assessment if such ideas were indeed forthcoming. So there must also be other ways of seeking out and deciding on the value of new ideas. In addition, the increasingly uncertain environment can make people feel uncomfortable. Some cling to or create procedures to achieve a sense of order and certainty.[8,9] For this reason, stage gates and the decision criteria posed within must be viewed as guidance to inform decisions, and they must be continually reviewed and updated in light of emergent information. If not, they become empty rules, comforting procedures that achieve the opposite from what they were intended for.

## Beyond stage gates

Costs can be reduced through the use of stage gates merely by the fact that key decisions can be taken earlier, at lower cost. In addition, well-defined and chosen stage gates allow effective operational alignment with strategic direction. However, stage gates are unable to address a fundamental problem: driving greater overall efficiency of the R&D operations. Strategic planning, benchmarking and reviewing practices in other industries are examples of tools employed. This can provide a forum to generate ideas on how to achieve more efficient ways to generate and analyse data, run studies and integrate R&D processes. As part of the planning process, creativity and innovation should not just be guided in connection with the end product – a new medicine – but also in the context of facilitating the discovery and development of these entities in an increasingly competitive and constrained environment.

## CONCLUSION

Stage gates can be one of many tools to channel creativity and reduce risk, thus increasing the rate of innovation in the pharmaceutical industry. They are not as helpful as enablers of much required creativity for coming up with fundamentally new ways to increase efficiencies or to guide creativity towards novel R&D strategies or radically different types of products. They can, however, help to define and create advantage, as well as find and deploy enabling technologies to demonstrate advantage. Stage gates are not a panacea, but they go a long way to facilitate the planning aspect of managing creativity while reducing costs. Yet, stage gates can be counterproductive for more intuitive forms of creativity, unless carefully used. They should therefore not be seen as an 'automated' rule system, but rather as a company-specific, powerful knowledge management system that can promote cross-functional learning and informed decision-making. Stage gates cannot and should not replace other forms of planning. Especially in the area of efficiencies through process integration, and radical new treatment modalities, additional strategies are needed.

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