Innovation deficit revisited: reflections on the productivity of pharmaceutical R&D

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Consolidation continues to be a major feature of the pharmaceutical industry, largely due to the impact of the 'innovation deficit'. The author performs a healthcheck on the industry by examining recent productivity in the industry in terms of the number and quality of new chemical entities introduced in 1996 and 1997. He argues that compared with an earlier projection of statistical data assembled for 1993, the industry situation appears better than was expected, however, the fundamental problem of an innovation deficit remains.

In 1995 and 1996 we published an analysis of the pharmaceutical industry's future productivity[1]. The study was based on a simple approach. We counted (or estimated) the number of preclinical research projects that were conducted by the top 10, top 20 and top 50 pharmaceutical companies in 1993. By assuming an average development time of six years, an average turnover time for the research portfolio of four years, a success rate of 40% for the transition of compounds from research into development and a success rate of 10% for the transition of compounds from development to market, we estimated the number of new compounds that the top 50 companies would be able to launch between 1999 and 2002. Our mathematical analysis produced a result that would not be sufficient to sustain the growth expectations of the industry.

By assuming that an average product generates annual sales of $400 million six years after launch and has a 17 year life span, we could then calculate the number of new substances that the industry would need to produce to sustain various growth rates. When we subtracted this number from the annual number of new drugs produced (i.e. deemed possible by the given number of existing research projects in 1993 and the historical success rates of development compounds), we arrived at what we called the 'innovation deficit' of the industry[1,2].

It was predicted that biotech products would be able to compensate for part of this deficit, but would be insufficient to fully make up for it – at least not in the time frame between 1999 and 2002. In many companies this analysis, which was corroborated by some similar studies, was perceived as a strong indication that the industry would have to increase its research productivity in order to escape the negative consequences of an insufficient innovative base. In fact, the broadly shared view that drug discovery would have to be reconfigured altogether and not just 'improved' to achieve the necessary increase in productivity appears to have influenced the determination with which large pharma companies embrace new technologies such as genomics, cell-based assays, combinatorial chemistry and high-throughput screening – technologies commonly seen as the elements of such a paradigmatic change in drug discovery.

Analysis of the industry

In view of the general awareness that the industry seems to have of its problem, the question was asked whether the productivity of the top 50 pharmaceutical companies, which formed the sample on which our previous study had been built, was showing any signs of improvement or

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whether it was still following the patterns that could be predicted from the 1993 figures. To view the situation of the pharmaceutical industry in 1996 to the present time, the following sources were used:

- The list of new drugs that reached their first market in 1996 (Ref. 3).
- The analogous list of drugs reaching the market in 1997 (Ref. 4).
- A list of prescription medicines for which documents were filed with the FDA between 1 January 1998 and 1 April 1998. It is expected that many of these drugs, which represent the most recent output of the international pharmaceutical and biotech industries, will be launched in the USA in the course of 1998 or early 1999 (Ref. 5).

For counting the total production of all pharma and biotech companies that launched prescription medicines in 1996 and 1997 and those they are about to introduce in 1998 and 1999, we classified the drugs as either new chemical entities (NCEs), line extensions (LEs), new drug delivery systems and formulations (NDDs), niche products and combinations, diagnostic drugs, or vaccines. The group of NCEs was further subdivided into three categories – A, B and C as in a previous study[6]:

A Includes all novel structures or novel applications of known structures. To be grouped into this category a drug had to promise a significant medical advance in an important disease.
B Drugs that represent one or several documented advantages over other similar drugs.
C 'Me-toos' – drugs that do not seem to offer any distinction from existing therapy.

Interpretation of results

The total number of new drugs reaching their first market in 1996 was 83. The classification into the various categories is shown in Table 1 along with corresponding figures for 1997 and the number of drugs approved or expecting approval for the US market in 1998. As can be seen there is a clear increase in drugs and drug uses from year to year. However, NCEs constitute only ~50% of these figures, despite showing an increased productivity from 46 in 1996 to 53 in 1997 and to 40 approved or filed for 1998 (Table 2). The remainder is represented by LEs, NDDs, specialized products, combinations, diagnostics and vaccines – in fact, it is quite remarkable how many of these have been launched at a time in which the global introduction of major NCEs has been the call of the day within the industry.

Our previous study published in 1995 and 1996 (Refs 1,2) was based on the top 50 pharma companies of the world. When we consider how many NCEs can be attributed to this group of companies in the three years that are under study here, the result is quite sobering: in 1996 the number was 32, in 1997 it came down to 25 and in 1998 it stands at 57 (Table 2). The 1998 figure does, however, include compounds like quazinone (Posicor), which was withdrawn from the market, tasosartan (Verdia™), for which the application was withdrawn, and ziprasidone (Zeldox), for which approval was denied. Thus, the real figure for 1998 is likely to be lower than 57 NCEs; nevertheless, 1998 appears to be a productive year for the pharmaceutical industry, with important launches in several therapeutic areas.

Input from small biotech companies

The proportion of drugs from the biotech industry appears rather high in 1998. Out of the 57 NCEs (launched or planned to be launched), 15 represent biotechnological

Table 1. New drugs introduced or nearing launch

Year	NCEs[a]				LEs	NDDs	Combinations/ niche products	Diagnostics	Vaccines	Grand total
	A	B	C	T						
1996	9 (1)	22 (3)	15 (1)	46 (5)	7	5	10	7	8	83
1997	12 (2)	18 (3)	23 (1)	53 (6)	3	12	20	8	1	97
1998	22 (8)	19 (4)	16 (3)	57 (15)	15	8	11	8	5	104

[a]A, includes all novel structures, or novel applications of known structures. To be grouped into this category a drug had to promise a significant medical advance in an important disease; B, drugs which represent one or several documented advantages over other similar drugs; C, me-toos. Drugs that do not seem to offer any distinction from existing therapy. This classification was only performed for new chemical entities (NCEs); T, total NCEs; the number of biotech drugs are given in parenthesis. LEs, line extensions; NDDs, new drug delivery systems and formulations.

Table 2. NCEs launched in 1996 and 1997 or intended to be launched in 1998 by the top 50 pharmaceutical companies[a]

Category	1996	1997	1998
A	6	2	15 (4)
B	15 (1)	13	15 (2)
C	11 (1)	10	10 (1)
Total	32 (2)	25	40 (7)
Grand total launched or filed by Universe	46 (5)	53 (6)	57 (15)

[a]A, includes all novel structures, or novel applications of known structures. To be grouped into this category a drug had to promise a significant medical advance in an important disease; B, drugs which represent one or several documented advantages over other similar drugs; C, me-toos. Drugs that do not seem to offer any distinction from existing therapy. This classification was only performed for new chemical entities (NCEs); the number of biotech drugs are given in parenthesis.

contributions of which eight represent major advances, four can be classified as improvements and three are me-toos. Only seven of the 15 biotech drugs come from or are marketed through one of the top 50 pharma companies, while four important new biotech drugs and two additional ones that represent improvements, have been developed and launched by companies that are not members of this elite group (Box 1).

The share of biotech drugs among the 53 NCEs reaching the market in 1997 was modest: only six drugs were found. Of these, Rituximab and Zenapax – two monoclonal antibodies, one for the treatment of B cell lymphoma and the other an immunosuppressive – were classified as major advances and both initially came from small companies but are now marketed with the help of major pharmaceutical organizations.

In 1996 only five new biotech drugs were listed out of a total of 46 NCEs. The single one classified as A, RespiGam – an antibody preparation against respiratory syncytial virus (RSV) – came from a small company, Medimmune (Gaithersburg, MD, USA).

NCE output by major pharma

Looking at the overall output of the pharmaceutical industry in the years 1996, 1997 and 1998, one could be impressed by the number of NDDs, niche products, LEs, vaccines and diagnostics (in other words drugs that are usually not NCEs) that have been introduced. However, the number of NCEs provided (not necessarily found) by the big pharma companies in these years are only 32, 25 and 40, respectively, which represents ~70% of the total industry's output in 1996 and 1998 and ~50% in 1997. If one restricts the analysis of the top pharma companies to innovative compounds, classified as major advances or definable improvements (A and B), the result is even more modest. The 50 big companies launched 21 innovative products in 1996, 15 in 1997 and they are about to launch (or have launched) 30 novel compounds in 1998, six of which are biotech compounds that were discovered by smaller companies.

Even if one includes all NCEs launched by the top 50 pharmaceutical companies in 1996, 1997 or about to be launched in 1998, the average number of compounds per company is well below one new drug annually. For 1996 it was 0.64, for 1997 it was 0.5 and if all drugs filed for approval were successful, the 1998 figure would be 0.8 NCEs per company. These numbers are higher than we expected on the basis of our previous calculation (i.e. extrapolated from the statistical values of 1993), but they are still too low to avoid the NCE gap or innovation deficit altogether[2].

Box 1. Biotechnology compounds about to be launched in 1998

Top 50 pharmaceutical companies
Sold but not invented by large pharma companies:

- Apligraf (manufactured human skin)
- Avakine (infliximab)
- Denileukin (DAB389IL2)
- Integrilin (eptifibatide)
- NovoSeven (eptacog α, activated; recombinant factor VII)
- Simulect (basiliximab)
- Synagis (palivizumab)

Smaller companies
Marketed by smaller companies:

- Adcon-L (carbohydrate polymer)
- Curosurf (porcine lung surfactant)
- Dermagraft (human dermal replacement)
- Fomivirsen (antisense molecule)
- Myotrophin (mecasermin, recombinant human insulin-like growth factor I)
- Rebif (interferon β-1a)
- Stemgen (ancestim)
- Thymoglobulin (rabbit antihuman thymocyte immunoglobulin)

The creative output of large pharmaceutical companies leaves much to be desired. On average, it is in the range of 0.5 to 0.8 NCEs per company, rather than the projected two or three compounds annually that some of the major players have announced to be soon achieving. The contribution of the biotech industry, although visible, is more modest than expected. In 1996 and 1997 it represented ~10% of the total output; in 1998 it seems to have risen to >25%.

R&D expenditure

Together, the top 50 companies command revenues of more than $180 billion out of an audited world market of roughly $240 billion. Assuming an average rate for R&D of 15% of sales, the total amount that these companies are spending for R&D is $27 billion. The real figure is likely to be higher because the top 20 companies tend to spend a higher proportion of their sales on R&D than 15%. Today's productivity cannot, of course, be related to the current R&D expenditure, but ten years ago, the total R&D expenditure of the top 50 companies was already in the range of $15–20 billion annually. These costs have been increasing to the present level rather gradually. If one relates an R&D expenditure of $15 billion to an output of 21 innovative compounds ten years later, the cost of each single compound would be around $750 million without any interest on the capital expenditure.

Final analysis

Although the time frame chosen for this interim analysis is short, the figures that are available today do not indicate that the large pharmaceutical companies have solved their research productivity problem. The figures of 1998 and also the quality of some of the medicines launched recently or about to be launched in the immediate future give some encouragement, but this optimism, which is often voiced by the industry's manufacturers' associations and lobby groups, is largely unfounded. Many large pharma companies continue to have a serious R&D productivity problem. The results of this small study can be summarized as follows:

- The overall number of novel and NCEs produced or made available through the top 50 pharmaceutical companies is too small to sustain a healthy growth of this group.
- It is too early to tell whether the increase in new drugs reaching the market in 1998 (and 1999?) signals a sustainable increase in productivity.
- The share of biotech drugs and the total output is significant but more modest than expected.
- The new technologies like genomics, combinatorial chemistry, cell-based assays, automation and bioinformatics do not appear to have had a major impact on the provision of new drugs by the pharmaceutical industry so far.
- The number of novel NCEs produced by the pharma industry continues to represent only a small proportion of the total output of drugs and new drug applications.

In view of these sobering facts, a continuation of the consolidation process that has been going on in the pharmaceutical industry should be expected. If the number of new compounds that are about to be introduced in 1998 could be sustained over the ensuing years, the problem of innovation deficit would be reduced by about one third. To eliminate it altogether, however, a further increase of productivity would be necessary. Of course, this increase need not necessarily come from NCEs alone; it could also be provided by LEs, NDDs or by synergies between diagnostic agents and therapeutics. However, given the structure of the health care markets today, the safest way to a higher productivity appears to be the launch of more unique and valuable NCEs for therapeutic purposes. At least for the next decade this will remain a major challenge.

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In short…

At a price of ~$11.9 million, **Corixa Corporation** (Seattle, WA, USA) has recently completed the acquisition of **GenQuest**, a privately held, oncology-based, functional genomics company. GenQuest uses functional genomics and differential gene expression to discover genes associated with cancer, response to DNA damage, senescence, cellular proliferation and terminal cell differentiation. It is beleived the acquisition will further Corixa's capability to develop antibody therapeutics and diagnostics.