'The capability exists to double both the output of manufacturing using existing assets and the effectiveness of R&D expenditure.'

editorial

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Patient heal thyself

The global pharmaceutical industry is rightly proud of its achievements – many years of successfully developing new drugs that have significantly extended the lives of many people and share prices that recognize excellent financial performance. However, despite these successes, the industry is under pressure from governments that wish to reduce the cost of drugs that draw on the health budget, third world countries that require lower price drugs for their economic situation and the growth of generic manufacturers. In addition, several consecutive years of falling numbers of Investigational New Drug discovery filings and new molecular entities approved by the FDA have compounded the challenges facing the industry. All these factors have had an impact on declining share prices and greater pressures on pharmaceutical companies.

The potential to improve operational, research and development performance

In 2003, I published a paper [1] that 'benchmarked' the operational performance of pharmaceutical companies. This compared the average operational performance with the best performance in the pharmaceutical industry, and also with that of the food industry (Table 1): definitions of the performance metrics highlighted are available in [2].

The message from this benchmarking was clear – if all the pharmaceutical and manufacturing companies in the world were to move from the average performance to that of the best in the industry they could double the output of existing assets, liberate a one-off cash release from stock of US$76 billion and significantly reduce the requirement for future capital spending. This might not surprise people familiar with pharmaceutical operations, where the nature of the process and varieties of forms of final product leads to inefficient operational behaviours. In addition, the characteristics of the investment patterns tend to lead to the under-use of substantial amounts of equipment. In the early days of the industry, this was not a priority, but with the pressures from generic manufacturers and others the necessity to release this 'hidden plant' is increasing.

The results generated from the application of the same benchmarking approach to the R&D process, stimulated by a request from the European Union for European Pharmaceutical Science, were a considerable surprise. The pharmaceutical industry is almost unique in that the performance of individual R&D departments is a significant component of the company share price, and new drug pipelines regularly appear in the financial papers. One consequence of this is that global financial analysts such as Goldman Sachs and Morgan Stanley effectively benchmark the performance of the R&D community. Pursuing this route, I was stimulated by the Novartis 2003 Highlights presentation by Daniel Vasella (Chairman and CEO of Novartis) to shareholders. This included a graph of benchmark performance for the R&D effectiveness of the pharmaceutical industry produced by Goldman Sachs [3]

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TABLE 1

Operational benchmarks

KPI	Pharmaceutical industry	A winning pharmaceutical plant	A world class plant
Stockturn	3–5	14	50
OTIF (%)	60–80	97.4	99.6
RFT (%)	85–95	96.0	99.4
CpK	1–2	3.5	3.2
OEE (%)	30	74	92
Cycle time (h)	720	48	8
Working hours without an LTA	1×10^6	2×10^6	10×10^6

Abbreviations: CpK, a process capability index; KPI, key performance indicators; LTA, lost time accident resulting in more than three days' absence from work; OEE, overall equipment efficiency; OTIF, on-time in-full delivery; RFT, right first time.

that identified Novartis as the most effective pharmaceutical company in this area: R&D effectiveness is measured using net present value and/or capitalized R&D, which is the present net value of the future drug streams divided by the capitalized cost of developing the new drugs.

An interpretation of the data from the analysis performed by Goldman Sachs (Box 1) is that the most effective organizations are seven times better at developing financially successful new drugs than the least effective. It also implies that if the average company in Europe were to move to the best in the world, then the effectiveness of new product development would improve by a factor of 2.33 (i.e. 2.1 divided by 0.9). The implications of this are enormous. Although this performance metric does not identify the practices exploited by the best companies to deliver this success, it does enable quantification of the potential impact. In simple terms, these metrics imply that if the average performance in Europe and/or the USA was to move to best performance, the cost of developing new drugs would approximately be halved. Thus, because the cost of developing a successful new drug discovery is reported to be ~US$800 million, they suggest that this figure could potentially be ~US$400 million or even less. Furthermore, this figure is already being achieved today in the pharmaceutical industry.

What does that mean? One implication is that the industry could either be using the existing capital accessible for research to produce twice as many successful new drug discoveries or be expending double the funds necessary to develop new drugs than if it adopted industry best practice. The answer is probably a combination of both options.

BOX 1

R&D effectiveness ratings

Most effective	2.1
USA (average)	1.1
European (average)	0.9
Japanese sector	0.8
Least effective	0.3

This data suggests that the pharmaceutical industry has the ability to use its available resources to satisfy many of the significant pressures identified. The capability exists to double both the output of manufacturing using existing assets and the effectiveness of R&D expenditure. Hence, the title of this editorial – 'Patient heal thyself'.

Learning from other industries

The present scenario facing pharmaceutical companies is a familiar story to other business sectors such as the motor, electronic, computer and food industries. In the 1970s, the car industry in the Western World was confronted with a similar challenge when competitive Japanese cars, manufactured using new techniques such as 'just in time' (JIT) manufacture and 'single minute exchange of dies' (SMED), entered the market. Thirty years later, Western manufacturers have adopted these techniques and responded through innovation, and the results are there to be seen in the outstanding quality and low prices of the products that they deliver. Along the way, the industry underwent significant restructuring, with the strong getting stronger, whereas many of the weaker companies ceased to trade.

Although the pharmaceutical industry often argues that 'we are different', this statement is only true with respect to the high degree of regulation – all industries initially make this statement. However, all other industries are regulated to some degree and, in terms of best R&D and manufacturing practices, the similarities far exceed the differences. Although I can understand why the leaders in the pharmaceutical industry would not wish to share their practices with their competitors (because it potentially provides a competitive advantage), I would suggest other industries would be willing to impart their best practices and experience.

Whereas the regulatory environment is different and demanding, the evidence suggests that the best companies within industry have already made the transition that will eradicate the problems encountered today, including satisfying the pressures imposed by governments, regulators and shareholders, and in the process move to a 'real-time release' [through process analytical techniques (PAT)]

environment. Over many years, it has been my experience that starting the journey to continuous improvement is the most difficult step. Once this step has been taken, the momentum builds and progress is made. Examination of the practices of other industries suggests a few initiatives that the pharmaceutical industry could implement:

- Develop and design new molecules and products on the principle that they will be manufactured on existing assets.
- Target to achieve a high (>90%) new product efficiency (NPE) at every stage of the development gate process: this is a demanding measure and our experience indicates that the achieved NPE is often considerably <90%. NPE is the product of:
  - (i) Availability: the percentage of 8760 hours year^{-1} that development is operating at full rate.
  - (ii) Product rate: best gate to gate time rate achieved as a fraction of actual time (expressed as a percentage).
  - (iii) Quality rate: percentage of all activities that are delivered right first time with no defects.
- Develop, design and operate for PAT: other industries already achieve PAT but it is often referred to as JIT manufacture.
- Focus on 'six sigma' quality targets at every phase and design quality into the product at the R&D stage.
- Assist manufacturing to achieve high overall equipment efficiency by standardizing product form, labelling and reduction of all non-value added activities.

It is easy to make these suggestions, but it is recognized that this transition will take time. Other industries have been on the journey for over 20 years, and they are still improving.

Focus on the pipeline processes and practices

In recent years, much has been discussed and invested in high-throughput experimentation (HTE). Is it heretical to suggest that this might have detracted attention from the key issues identified here? The paradox is that whereas HTE has been able to create new molecules at an enormous rate, progress in genomics has not really developed meaningful *in vitro* screening methods, and the rate of drug discovery filings and new molecular entities approved by the FDA is falling! Perhaps the answer is to concentrate less on the creation of new molecules and more on the pipeline processes and practices to focus research and reduce the candidate attrition rates.

I will end this editorial with a quotation I consider appropriate – 'Standing still is the fastest way of going backwards'.

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