What place for R&D in tomorrow's drug industry?

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The relative merits of just three strategies will determine the future of R&D. The pharmaceutical industry has embarked on a bewildering frenzy of restructuring; companies announce new acquisitions and alliances seemingly on a daily basis. However, taking a step back, there are only three 'mega-strategies' open to them. First, horizontal integration – acquisition of other pharmaceutical products through, for example, a merger; second, vertical integration – acquisition of customers, who may be distributors or even healthcare providers; finally, R&D. These are the strategies that are competing for investment funds. This article explores the real long-term promise in each of these strategies and the implications for drug discoverers and developers.

Healthcare systems vary enormously across the globe, but they have shared one thing in common for many decades: an inability to curb relentless growth in healthcare spending. During the last decade, however, new circumstances have allowed, or forced, something to be done.

We seem to have a problem

In the USA, a huge glut of physicians caused a power-shift from physicians to payers; managed-care got a foothold. Meanwhile, government deficits in Germany and Italy forced drastic action on government spending. In the UK, right-wing, market-oriented politics gave another incentive for radical change.

There is nothing really new in the measures that the market (in the USA) or governments (in Europe) have imposed. In the States, managed-care has been around, albeit as a marginal player, for decades. In Europe, a vast array of government measures to curb prices and costs has been a part of the landscape for as long as some can remember. It is the range and severity of price and cost controls operating in any given country that has increased.

It couldn't have come at a worse time

Just as burgeoning health cost controls are forcing down the rewards of pharmaceutical R&D (i.e. sales), so ever-tougher regulatory hurdles are forcing up R&D costs. As an indicator, the average number of pages per NDA grew from less than 40,000 to more than 90,000 in the course of the last decade. The cost of developing a new product (including the costs of capital and failure) has grown from an estimated $87 million in 1982 to more than $350 million in 1983[1].

It is not surprising, then, that the number of new product introductions per year has not increased. Indeed, just holding the number of introductions constant, which is what the industry has achieved, has resulted in R&D spending growing from 12% to 19% of sales between 1980 and 1994 in the USA[1]. Not only are R&D costs exploding, but other allied costs are growing fast as well. In particular, manufacturing (where overall costs are now higher than they are for R&D) is a strategic issue; major investments are required pre-approval.

Are we sure we have a problem?

In spite of this tougher environment, the pharmaceutical industry is one of the most profitable on earth, with returns on capital employed, pre-tax profit margins and returns on shareholders' funds around threefold those seen in other

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industries. These extraordinary profit levels flow from past investment in R&D, but will such a strategy be effective or sufficient from now on? Or, are horizontal and vertical integration better investments?

Is horizontal integration on the level?

There is nothing new in a frightened industry seeking safety in numbers. But the current wave of mergers does not necessarily mean massive industry consolidation. The top five pharmaceutical companies, between them, command a 16% share of the global pharmaceutical market. This is less than for any other major industry, and that proportion has not changed for decades.

Economic theory suggests that the pharmaceutical industry should not be a consolidated one. Consolidated industries tend to have a common core technology. For example, technologically, all cars and all microprocessors are similar and so these industries are highly consolidated. The technological base of pharmaceutical companies is highly fragmented and so is the industry.

Consolidated industries tend to have 'barriers to entry'. For example, it is prohibitively expensive to build a modern robotic car plant. However, a biotechnology company can be set up for a few million dollars and achieve sufficient progress to raise funds for the next stage of development. Indeed, there are currently around 1,400 biotechnology companies worldwide, and a new one starts up, on average, every seven days.

So much for theory, but what about practice? If this industry is consolidating, there must be evidence. If larger, merged companies are the future, then the benefits of merger should lead to a company that expands, or at least retains, its share of the global pharmaceutical market. The record does not support this. Every single major merger (recently and during the 1970s and 80s) has resulted in a company whose global pharmaceutical market share has declined.

The reason is that merging companies are usually facing a difficult future (with major patent expiries and/or barren pipelines). From 1991 to 1995, products with annual sales of around $16.5 billion have come off patent in the USA alone. It is the owners of these products that have merged and the consolidation from the merger is offset by the market share decline post-merger.

Waves of major patent expiries and the associated mergers will continue to wash across the industry. But there is nothing to suggest massive consolidation or that merger is an alternative to R&D.

Is vertical integration on the up and up?

Vertical integration has dominated the US pharmaceutical scene for the past few years as major companies have scrambled to buy up pharmacy benefit management companies (PBMs). PBMs work on behalf of managed-care companies (MCOs); they process patients claims for drugs, ensure that prescribers adhere to formularies and review the cost-effectiveness of prescribing.

Economic theory says that if you are a monopolist making monopoly profits (as pharmaceutical companies are, by virtue of their patents), you should keep integrating vertically as long as you are purchasing another monopolist. Once you reach a competitive market, however, you should stop, because competition, by definition, will prevent monopoly profits. Unless, that is, you can buy all the competitors – in which case you have a monopoly again. However, it takes much less than that to get the US antitrust authorities excited.

These two factors – competition and antitrust authorities – are certainly bearing down on PBM acquisitions by the pharmaceutical industry. Claims processing is fast becoming a commodity. MCOs are watching PBMs owned by pharmaceutical companies closely for signs of favouritism towards their own products. Antitrust authorities have insisted on open formularies and firewalls between PBM and pharmaceuticals operations to protect sensitive information on competitors.

Perhaps realizing that there is no profit bonanza to be had from PBM operations *per se*, the acquiring pharmaceutical companies have shifted emphasis from moving their own products' market share to the generation of outcomes – particularly health economic – data and to 'disease management'. Is this a sensible move or are they jumping out of the frying pan and into the fire?

The data captured by PBMs is messy. Their IT systems were not designed to run the complex algorithms required for outcomes analysis. They do not have access to diagnostic information, and although this can be collected from MCOs, it is often incorrect. All of which explains the recent comment in the *Financial Times*, 'the drug industry's diversification into distribution looks like an expensive mistake'.

So, vertical integration too, does not look like an alternative to R&D. Indeed, it may be more sensible to view it as an adjunct. Zeneca recently purchased 50% of Salik, a US cancer care provider. Zeneca, has focused less on building market share and more on using the acquisition to deepen understanding of cancer care to focus the company's R&D.

Buying a PBM at enormous expense may not be the way to address health economics or disease management, but this doesn't mean that these two concepts are not important and valuable.

Is health economics economic?

There is a long-running academic debate raging as to whether health economics is a valid subject. On the one hand, a *Lancet* editorial[2] says that doctors are in danger of knowing 'the value of everything and the price of nothing'. On the other, an editorial in the *Annals of Internal Medicine*[3] suggests that, '"pharmacoeconomics" has been conjured into existence by the magic of [pharmaceutical companies'] money'.

For the drug developers, the debate is academic. The fact is that health economics is starting to be a *de jure* requirement. Regulators in Ontario and Australia now demand health economic data. Elsewhere, it is becoming a *de facto* requirement. MCOs in the USA now insist upon clear evidence of the cost effectiveness of new therapies. Their dictum is 'In God we trust – others must bring data'.

What are the implications for drug developers? First, early commercial appraisal of drug development candidates must entail a clear understanding of the health economic impact that a new drug might have. The decision whether to develop the drug has to include a judgement on whether it will have a favourable economic impact.

Once that leap of faith has been made, a proof is required. This means building as much health economic data collection as is practical into regulatory studies. Above all, resource usage and quality-of-life data must be collected.

However, collecting these data is not enough. Consumers of health economic analyses want to know the impact of a drug in real life, not in a clinical trial. They will also require data in countries where trials are not conducted. In an ideal world, companies would conduct large, prospective 'naturalistic' clinical trials in parallel to phase III studies. In practice, they will probably end up modelling the real-life impact of the drug through a combination of protocol-driven phase III study results and expert-derived algorithms of what happens in clinical practice.

Early attention to health economics is vital, but this is a part of, not an alternative to, drug development.

Is disease management manageable?

Health economic data is an adjunct to other regulatory and marketing data, but the concept of disease management takes the health economic impact of a drug and seeks to turn it into a product in its own right.

A recent highly-priced report in disease management opened with a startlingly unequivocal assertion: 'Disease managers will become the new gatekeepers for medical care... leaving the majority of the industry under the control of the disease managers.' As is the case with every new fad, the grandness of the predictions are surpassed only by the vagueness of the accompanying facts. The report in question goes on to say that 'As yet there is no consensus view as to what disease management is'.

The range of competing definitions of disease management is bewildering. At one extreme, there is the dream as defined by a Coopers and Lybrand consultant at a recent *Financial Times* pharmaceutical conference, who said "An information-based process involving the continuous improvement of value in all aspects of care (e.g. prevention, treatment and management) throughout the entire spectrum of healthcare delivery." At the other extreme, there is the highly-pragmatic definition of a practitioner, Ray Gilmartin (Merck and Co), who says, "To us, disease management means treating diseases more effectively by using pharmaceuticals more effectively."[4]

The ways in which pharmaceutical companies are trying to get pharmaceuticals used more effectively fall into three categories.

The first is selling related products together (bundling). Some pharmaceutical companies have offered such packages. These range from drugs for diabetes and the associated diagnostic tools to a full range of anti-asthma medications. This approach is predicated on the notion that buyers prefer to deal with one supplier rather than many. There is certainly a trend in this direction as far as complex items such as laboratory equipment are concerned because of a desire to minimize the complexities of dealing with a range of suppliers, such as multiple service contracts. However, in the pharmaceutical industry, the appeal of this concept is much more patchy and tenuous.

The second area of activity can best be described as 'using a mackerel to catch a sprat'. The trick being, to ensure that the mackerel belongs to someone else. As an example, Lilly developed protocols with MCOs in the USA whereby generic cimetidine would be used as first-line treatment in ulcer disease, and their own drug nizatidine (Axid), would be used as second-line therapy. Axid would also be used as the first-line treatment in gastroesophageal reflux disease. The HMOs benefit from the genericization of the

high-volume, first-line H_2 receptor antagonist usage (the mackerel) and Lilly benefits from modest market share in its second-line positions (the sprat). There is isolated anecdotal evidence that this strategy has delivered some success.

The third and most important activity is making healthcare providers understand that unless they 'buy a cat they will have to feed the rats'. This is just marketing the reality that most healthcare costs are 'downstream'. In other words, they are the costs of hospital and terminal care that result when preventive and primary care fail. It is often far more cost-effective to make use of pharmaceuticals as preventive or prophylactic therapy than it is to pay for the hospital care that it can have prevent. A case in point is asthma; pharmaceutical companies have become involved in encouraging patients to take prophylactic pharmaceutical therapy – mainly inhaled steroids – to prevent what is the major cost in asthma therapy, emergency room treatment.

In practice, therefore, the activities that are grandly referred to as 'disease management' are a collection of marketing tactics, none of which could represent an alternative to R&D.

Do we need to develop development?

So neither horizontal nor vertical integration are likely to be viable strategies in their own right. Nor are the spin-offs of vertical integration: health economics and disease management. That leaves R&D. However, because regulations and technology are forcing R&D costs up, and cost containment pressures are forcing sales revenues down, R&D must become more effective within those companies who are going to continue to prosper.

The problem is (of course) that too few genuinely innovative drugs targeted at substantial patient populations are developed. The evidence suggests that there may have been a marginal improvement in the past decade, but not nearly enough has been done to counter the challenges that the industry faces.

To improve the situation, companies must think clearly about when to start and stop developing drugs. This thinking must be based on the hard facts of drug development:

- Only one in five drugs that enters development reaches the market.
- Only one in five drugs reaching the market generates sufficient return to cover the costs of development.
- As a drug passes through development, the costs of moving it forward rise exponentially. Not only is late development much more expensive than early development, but hugely expensive manufacturing and marketing commitments have to be made.

Given these hard realities, it is important to establish a rationale for investing in R&D. Early spend in development should not be viewed as a *commitment* to continue development. Rather, it should be viewed as the *cost of buying an option* to continue if things still look promising. If they do not, the project should be killed.

When a drug enters development, little is known about its future profile or about the shape of the market that it may enter nearly a decade later. Therefore, estimates of what the drug could be worth will span a very wide range; often, from zero to $3 billion. By conducting some early development work it is possible to buy two things. First, more and better information: a clearer idea of what the drug's profile *might* be. Second, the option of continuing to develop the drug. The range of sales possibilities should now have narrowed somewhat. Not only is more known about the drug, but the company has been able to track competitor and market developments. More informed guesses about the future range of sales possibilities can be made. Only if the expected returns for the product still exceed expected costs of developing, making and selling it should the option be exercised to proceed to the next stage of development.

By rigorously applying this approach, the decision to embark upon each (ever more expensive) stage of development is taken in the light of the fullest possible knowledge. Given that it is the later stages of development that devour most of the money, the degree to which expensive late-stage development is squandered on unpromising products is minimized – freeing up resources for tomorrow's breadwinners.

Although this sounds like a logical and obvious procedure for companies making these vast investments, a Center for Medicines Research survey of 49 leading pharmaceutical companies[5] revealed that more than half specified no minimum sales-level for products in development, more than one-fifth had no criteria for project termination and more than half had no standard operating procedure for project termination. The human foibles that lead to such bizarre decision making are a fascinating topic[6].

There are three major implications to applying the 'options approach' to R&D decision making. First, the most

valuable targets for discovery and early development may well be the ones for which there is great uncertainty regarding future sales potential. Options are at their most valuable in the face of a volatile and uncertain future (this is true of options in financial markets as well as in drug discovery).

Second, 'wish-driven' R&D strategies of the 'we will launch two NCE's a year' variety are counterproductive. They mean that a company is committed to exercising its options to complete development and launch products irrespective of whether it is sensible to do so in the light of ongoing trial results.

Third, there should be a shift in spend from late stage development to discovery and early development. Late stage development should be decreased because, as stated above, it entails the exercising of too many options to develop nonviable products. Discovery and early development should be increased because it allows a great many options to be opened relatively cheaply (this applies to the industry as a whole rather than to individual companies). The emergence of research boutiques could, in principle, assist companies to make this shift relatively quickly.

However logical this last point is, it is counter intuitive to many people. It is nevertheless sensible in any field of endeavour where the costs of creating the initial ideas are relatively cheap and the costs of fully prosecuting them relatively expensive. It has, for example, proven true in advertising where a shift in spend from running campaigns (very expensive) to generating ideas for campaigns (relatively cheap) from which the most effective is selected has been shown to boost the effectiveness of the advertising dollar overall.

Conclusion

The current penchant for horizontal and vertical integration is unlikely to add the sort of lasting value that effective R&D can deliver. Perhaps the industry could better be served by applying some good management practice to R&D than by throwing billions of dollars at such acquisitions.

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