The Future of Pharmaceutical Innovation: New Challenges and Opportunities

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Is the current pharmaceutical R&D model sustainable, and if not, can 'smart regulation' ensure that regulatory regimes are suitable for the emergent science, technologies and therapies that have the potential to transform healthcare and the industries that provide for it?

For more than a decade, analysts of the pharmaceutical industry have argued that the conventional blockbuster model of drug discovery and development is unsustainable, despite many years of investment in new life science technologies. Explanations have included a failure of innovation capacity and low productivity, a focus on incremental rather than radical innovation, excessive regulatory barriers and a lack of venture capital investment. However, an alternative argument can be posed that the pharmaceutical innovation model has been remarkably resilient and multinational companies have been extremely robust in maintaining their market dominance. Pfizer's recent announcement that it will close a major R&D site at Sandwich (Kent, UK) is a clear blow both to the North Kent regional economy and to the broader UK research base. Nevertheless, it illustrates a broader global trend in Big Pharma where large-scale merger and acquisition activity is followed by major company restructuring and R&D rationalisations as firms try to implement strategies to meet the growing demands of blockbuster innovation and sustain revenue streams.

In this article, we consider the sustainability of current pharmaceutical innovation strategies in the context of the challenges and opportunities posed by the life sciences. We argue that the regulatory system plays a predominant role in shaping innovation trajectories. We also consider the benefits of 'smart regulation' and conclude with some comments about the future of the big pharma sector. Our key question is whether the pharmaceutical R&D model is sustainable and, if not, what alternatives are available.

THE PROBLEM OF MATURITY & THE EMERGENCE OF CRITICAL 'TIPPING POINTS'

In a recent editorial in *The Lancet*, the retiring head of the European Medicines Agency (EMA), Thomas Lönngren, is quoted as stating that the drug industry is wasting more than half of its R&D investment given how few new molecular entities are being produced (1). In the same article, the CEO of GSK, Andrew Witty, points out that shareholders are no longer prepared to see money invested in R&D without tangible success.

The pharmaceutical industry is continuing to face a number of innovation challenges – low productivity, patent expiry, rising costs of R&D, high attrition rate of compounds in Phase 2, high regulatory hurdles, increasing concern about adverse side effects and so on. But a major challenge that is often ignored is what we call the 'problem of maturity' (2). By maturity, we mean that drugs have already been developed for all the easy targets, and now that they are off patent, they no longer attract the high profit margins necessary for sustainable growth. It is increasingly difficult to find novel products that are effective enough to compete with existing product ranges, safe enough to pass regulatory scrutiny, cheap enough to manufacture, as well as cost-effective enough to meet reimbursement requirements. These factors – rather than complacency or endemic failure of innovative capacity – play a major role in the drying up of product pipelines. In turn, they lead to waves of merger, acquisition and strategic alliance behaviour, and recurring experiments in organisational restructuring (3,4).

The question then becomes why, given these pressures on the conventional R&D model, has big pharma remained apparently sustainable for so long? Our research over the past decade has highlighted the important and predominant role that the regulatory system plays in life science innovation – more so than almost any other industry sector. Although regulation has a direct impact on product development, we suggest that the impact is more far-reaching than simply ensuring products are safe and effective. Regulation essentially determines company strategy, the types of firm able to bring products to market and the structural dynamics of the sector as a whole. Under current circumstances, this is a barrier to the successful development and delivery of truly innovative technologies and therapies that could move the sector on to a high value-added innovation trajectory. Instead, change in the sector has largely been incremental (5). Tait *et al* have argued that the industry is heading for a 'tipping point' at some time in the near future, which

could lead to the fundamental disruption that seems necessary and inevitable – but also perhaps unimaginable (6). Regulation, because it is has not been flexible and adaptable, acts to reinforce a situation whereby current blockbuster innovation models are unsustainable, but discourage new developments that could bring about necessary change. Nobody can yet predict the eventual trigger for change, nor the outcomes in terms of winners and losers.

THE NEED FOR 'SMART REGULATION'

The key challenge for ensuring that necessary structural change in the sector is manageable, is the construction of smarter regulatory approaches that are more responsive to the opportunities emerging from the life sciences and do not simply support the status quo of multinational dominance. At present, the lengthy, expensive and demanding nature of the drug regulatory system is sustaining the unchallengeable supremacy of the Big Pharma companies. The high costs and long delays of taking a product through the cumbersome regulatory system ensures that only the largest companies are able to operate throughout the innovation life cycle. For novel technologies or products that may disrupt conventional Big Pharma strategy, such as stem cells, it is difficult to identify a route to market for the smaller companies that are at the forefront of developing the science.

Regulatory systems can, over time, become dysfunctional and out of step with changes in the science and technology that they regulate. Furthermore, as regulatory systems evolve, they can become so complex that any change or addition to one set of regulations can have unpredictable consequences for other parts of the system and the companies affected by them. As a starting point for further discussion in this area, we draw a number of lessons for better regulation of the life sciences.

First, since regulatory initiatives can have a transformative impact on innovation (both positive and negative, but also unpredictable), sensitivity towards the impact of regulation on particular industry sectors and innovation strategies is crucial when designing or re-designing regulatory systems for novel therapies that have no established route to market.

Second, because regulatory change in one policy area can have unexpected consequences for other policy areas, or even entire innovation sectors, it is vital that regulators are made aware of potentially useful but vulnerable products and processes under development, and their location within broader innovation networks.

Third, smart regulatory systems will always strive to enable positive changes in innovation strategies and adequately discriminate among products on the basis of socially and economically relevant criteria, as this will be more effective and efficient than an indiscriminate strategy that simply tries to constrain undesirable behaviour. An enabling criterion will positively affect the speed of the regulation's influence. The appropriateness of its product, or process discrimination will determine its effectiveness in guiding product development in desirable directions.

Finally, the development of path-breaking regulation for path-breaking technology should always be a last resort. When considering which regulatory option is most appropriate for a new, innovative technology, a good default rule would be to invoke the regulatory system in operation for the industry sector for which the innovation is path-dependent, rather than path-breaking.

If we embrace the philosophy of 'smart regulation' – which does not necessarily mean less regulation – expected standards of safety and efficacy can be delivered and new market opportunities can be opened for smaller companies. Big Pharma may also be enabled to pursue a more sustainable product development strategy.

CONCLUSION: THE FUTURE OF BIG PHARMA

It is conceivable that the pharmaceutical multinationals will continue to survive in their present form and pursue the same strategies of small molecule blockbuster innovation, which will involve further waves of large-scale mergers and acquisitions, and the subsequent disruption of asset-stripping and R&D rationalisations. However, the innovation model is being undermined not only by the problem of maturity, but also through regulatory and market challenges – with demands for cheaper drugs, regulatory changes encouraging drug development for small niche markets and stratified patient sub-populations, and an increasingly negative public image of the sector as a result of high-profile product withdrawals. True blockbuster products are simply becoming ever more elusive.

If disruptive change in the pharmaceutical innovation model does become inevitable, it will be important to manage this change carefully if we are to ensure that continued medical benefits are delivered to patients. The key to achieving this is through the regulatory system, and any regulatory change must be accompanied by a good understanding of the subtlety and complexity of the interactions between regulation and innovation in the life sciences. Among other things, this will require a commitment to smart regulation that looks at the very nature of particular regulatory regimes and ensures that they are suitable for the emergent science, technologies and therapies that have the potential to transform healthcare and the industries that provide for it.

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