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Making Drugs Safer Might Cost You Your Job – or Even Your Life!

On the 1st February 2011, one of the largest and most successful global pharmaceutical companies, Pfizer, announced the closure of its Sandwich (Kent, UK) site, with the loss of the 2,400 jobs. Some, such as John Gapper at the Financial Times, see this as another step on the road to the complete out-sourcing of drug discovery by the major pharmaceutical companies. And even the most bullish industry commentators don't see this as the last downsizing of R&D in the sector.

The trend to reducing big pharma R&D spend on "conventional" drug discovery seems inevitable. The return on this investment is likely to be punishingly low (if you calculate it properly, it is the return seen 10 years from now set against today's R&D expenses that you need to project, not today's returns, based on R&D done a decade or more ago, on today's investment). But the bigger question has to be "why is this?" Its easy to assume its because big pharma are not very good at early stage discovery, and that out-sourcing will lead to an efficiency gain - better pipelines at lower costs.

To a degree, it probably will do (that is, after all, what you get for out-sourcing many non-core activities - and discovering blockbusters is not the core competency of big pharma: their competencies are in marketing and in late stage clinical development). But there is a much bigger factor in play here...

“There is an ethical paradox that lies at the heart of declining R&D investment”

Society's attitude to the risk:benefit trade-off in medicines has changed beyond all recognition in 20 years. In fact, society's attitude to risk in all its forms has changed in this period, with wide ranging and almost entirely negative consequences. Whereas risk was once seen as part of life in every sphere, today the focus is on removing risk – whatever the cost of doing so.

Investment in new rail infrastructure following the Hatfield rail crash in October 2000 was just one high profile example of this trend: while any accident is regrettable (and much worse than that if you or your family happen to be involved), a response that involves spending millions to try and prevent a similar event ever from happening again can only driven by political expediency. By any rational measure, the same investment could have saved many more lives had it been directed at almost any other project.

Sometimes the cost of reducing risk is more indirect, and therefore less obvious. Laudable attempts to eliminate discrimination (whether on the grounds of race, gender or sexual orientation) from the Police force are a good example: the positive effects of the policy are easy enough to measure, but the cost (in terms of paperwork to be filled in to monitor behavior) are largely hidden. How many less criminals are we prepared to catch in order to be certain that undesirable discrimination is almost entirely eliminated?

Sometimes this apparently sensible elimination of risk harms the very people it is designed to protect. Half a century ago, county agricultural shows in the UK were a highlight of the calendar for the poorer classes – a chance for a day out without breaking the family budget. Today they are very different affairs: modern toilet facilities are provided, while the whole event is heavily policed to ensure public order. In short, the quality and safety of the event has been improved in every area. But as a result the price has gone up until it is all but out of reach for the people who valued it as part of their community fabric. No-one did more than the last Labour government to take away opportunity for the poorest in society simply by legislating to drive up standards.

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One of the biggest problems with eliminating risk is the non-linear relationship between cost and benefit. No matter what area of life you examine, as you approach 'completely safe', each tiny improvement in safety comes at an increasingly high price. Squeezing out the last drops of risk costs exponentially more.

This risk reduction mantra has dominated the regulatory agenda for pharmaceuticals as well. Regulatory authorities are on a crusade to reduce risk as far as humanly possible on behalf of a grateful populace. And that's the dominant factor that makes investing in new medicines such a poor long term investment.

Who could question the objective of making medicines safer and safer (or, for that matter making railways safer or reducing police discriminatory behavior)? We all should. The consequence is that developing new medicines is becoming economically unsustainable.

Who will suffer? You and me. The drug companies will morph into something else, using their current cash cows to achieve that transition (and we see the first phases of these changes happening already: GSK, for example, are increasingly focused on over-the-counter products and vaccines rather than traditional patent-protected medicines). But if the big drug companies withdraw from the front line of drug discovery, we are left with fewer new medicines.

“If you demand zero risk then some perfectly good medicines will be rejected by the regulatory authorities – and before long others will be killed by their owners before they consume the vast cost of late stage development”

Like the unintended consequences of government policies to drive up standards that disenfranchise those too poor to afford the resulting level of quality, in the same way reduced registrations of new drugs is an unintended consequence of demanding ever greater levels of safety.

Unfortunately, the cost of improving safety still further are largely hidden – it's the loss of an otherwise beneficial drug from the development pipeline because the implications (in terms of money and time) of demonstrating safety to the current threshold required by the regulatory authorities simply makes continuing to invest in that product too risky. The attrition rate during clinical

development ratchets higher: both because drug candidates genuinely fail to meet the new standards of safety, but almost as often because the cost of demonstrating the required level of safety is simply prohibitive. Increasingly, there are vast areas of medicine where the economic model for a product is now so unattractive, no-one even contemplates initiating a discovery or development process in that field.

This attrition then manifests itself in the falling returns on capital from big pharma and in the low rates of new approvals for genuinely first-in-class medicines. If you demand "completely zero risk", perfectly good medicines, with perfectly sound risk:benefit trade-offs start to get rejected by regulatory authorities and, before long, get killed by their owners at an early stage before they consume too much of the massive R&D costs of late stage development.

“If you want to understand why investment in healthcare R&D is declining, you need to look at society’s attitude to risk, and how this is reflected in the behaviour of regulatory agencies”

Of course, its easier for policy makers and commentators on the industry to blame falling approvals and falling returns on capital on the structural inefficiencies of research in a large company environment. For outsiders, its simpler to assume the problem is that big pharma just are not good enough at drug discovery and development. Its just too obvious that improving safety is a desirable goal, while the costs of the relentless pursuit of that objective are just too well hidden.

But if you want to understand why Pfizer took the decision they did, and why John Gapper at the FT predicted the decline in R&D at big pharma, you need to look at society's attitude to risk and how this is reflected in the actions of regulatory agencies that are, in the end, public servants. Without a sea change in how we approach drug regulation (and indeed much else in life) in the future, the current trend will be the tip of the iceberg. As investment in new medicines bleeds away, many of those currently employed in the industry will find themselves looking for a career outside of healthcare, and many of those with incurable illnesses will lament the lack of progress. Bizarre as it seems, demanding ever safer drugs really could cost you not only your job but also your life!

