



## Hard Times, Harder Times

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No one is in any doubt that these are hard times for life sciences companies. Some commentators have even suggested that these are the hardest times. The cause is obvious enough: the paucity of capital that has blighted the 'real' economy has been felt even harder in the cash-hungry world of technology companies that lack any kind of revenue stream to help weather the storm.

But to attribute all the woes of the biotech industry to the credit crunch would be too simplistic. Even as access to capital increases, and investors' appetite for risk returns towards the long-term average, the troubles for life sciences companies may ease slightly but they will not go away. The baseline has changed for good, and there will be no quick route back to the gold rush days of the 1990s. Learning to play by the new rules will be an essential factor in the survival of the fittest life science companies.

Leaving aside the current (and hopefully transient) shortage of investment capital, which is a problem not restricted to biotech, there are at least four factors which contribute to the distinctly chilly climate for healthcare commercialization in the next decade.

The first is payor pressure. As far away as preclinical drug discovery is from real paying customers (and there is no industry on earth which is further removed from its consumers), the entire healthcare value creation chain is affected by the change in attitudes of the big healthcare providers, be they governments or private insurance behemoths. A seismic change in the balance of power between the drug companies and their customers has taken place in the last few years, and the pace of that change is only accelerating. If purchasers are prepared to pay less, then the ripples will be felt right down to the owners of early stage healthcare technologies. Large pharmaceutical companies are adapting as fast as they are able, focusing on delivering value for money rather than small incremental benefits that have, in the past, attracted a scarcely-earned premium in the market place.

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For the biotech industry, whose real customers in almost every case have always been the large pharmaceutical companies, this represents a big challenge (and for the lucky minority, something of an opportunity). The shopping list of big pharma executives has shifted faster than the biotech life cycle – so if the product you are developing no longer meets the elevated "value for money" hurdle, the challenging but plausible exit you once sought may rapidly be turning into mission impossible. As a result, a mountain of relatively late stage technologies are accumulating that will never see the marketplace, despite "working" at least by the measuring stick of the last decade.

This process will only continue, and biotech entrepreneurs selecting early stage assets for development can no longer do so without due regard for the demands of the final customer – the healthcare provider. And far less early stage technologies have that potential, which means a smaller, leaner healthcare sector developing a smaller number of higher value products will surely begin to emerge.

And the opportunity? For those fortunate enough to hold assets with real potential to provide “must have” products offering stepwise rather than incremental healthcare benefit may see the value of those assets rise (or at least fall more slowly) compared with the bulk of what is being peddled at the present time.

The second factor is the biotech business model, which has seen the sector as a whole yield disappointing returns to investors not just in bad years, but over an extended period. For a while (perhaps for too long) the inferior returns of the sector have been disguised by some very visible successes – individual companies returning ten-fold or higher returns on their initial investment. This allows investors to believe that it is possible to substantially outperform the disappointing average ‘simply’ by being smarter than the rest, and spotting the winners at an earlier stage. But even the most optimistic investors are beginning to doubt their ability to pack their portfolios with the solid gold companies. There are easier ways to beat the biotech sector average – simply go invest in something (almost anything) else with better company fundamentals.

### **The Four Factors**

1. Payor pressure
2. Biotech funding model
3. Patenting landscape
4. Regulatory climate

What lies behind these systemically poor returns? To a degree, it’s the same thing that underlies the many woes of free market economics: markets are only efficient at setting prices over the short term – the longer the gap between value realization and price setting, the greater the errors in market valuation. These distortions are everywhere. Long-term damage to the environment is not factored into the price of natural resources and

increasing longevity is factored into pension costs too slowly. Similarly, too high a proportion of the value created by developing innovative healthcare products is captured by the entities that bring those products to the marketplace. Late-stage developers have to invest larger sums of money, but they do so at lower risk than the early stage investors, yet the price of early stage assets in the marketplace does not provide a sufficient return to account for the risk taken by those early investors, with the price kept low by the power of the purchasers.

As a result a funding chasm has opened up. Research, supported by governments and private backers such as medical charities, continues to spew out opportunities while at the other end, large pharmaceutical companies are increasingly desperate to acquire revenue-generating products. But while the returns are so poor, fewer and fewer investors are prepared to take the risk of backing the transition from promising idea to commercial product candidate.

Once again, therefore, this is leading to a much more careful selection of the research opportunities that are going to receive investment backing. Entrepreneurs using the old rule-book to identify fundable opportunities are likely to be disappointed, and companies left holding part-developed or tarnished early-stage assets will find new investment impossible to attract (at least on terms that attribute any value to past efforts) even when capital is once more freely available.

Today, we are seeing the few remaining investors in this area attempting to cherry-pick the best early stage assets to move them through the value creation chain much more cheaply than in the past. Virtual early-stage development companies are proliferating and the 1990’s grand glass-fronted biotech headquarters may never return. If this results in higher quality assets being selected and moved forward quickly and at lower cost than in the past, these investors will see returns that exceed past disappointments, and a leaner, meaner biotech sector will emerge. If it proves impossible to pick the better opportunities despite the input of a new breed of experienced, entrepreneurial high-caliber scientists, then life sciences commercialization will meet its Armageddon, and who knows what will emerge on the other side.

The role of these two factors in shaping the new biotech landscape have been widely recognized and discussed. The other two factors are just emerging, and while they have the potential to be equally damaging as the first two, investors and entrepreneurs alike are only just beginning to consider their impact.

The first of these 'new' factors is the changes in the procedures for obtaining patent protection. Intellectual property lies at the heart of the therapeutics value chain because it represents the tradable commodity. Investment adds value to the core intellectual property, usually in the form of patents or (for early stage technologies) patent applications, which is then sold on (hopefully for a higher price than the cost of building the asset) to the next player in the chain.

For a couple of decades, the patenting landscape was relatively benign, as a system designed to protect widgets was exploited to protect complex pharmaceutical "knowledge". The number of granted patents covering technological innovations grew exponentially providing the fuel to power the golden-age of technology investing.

Rightly, however, this patent "land grab" has gradually come to be perceived as having gone too far. Granted claims have often been poorly reduced to practice across their entire scope, and have served to inhibit genuine innovations in broad, and very promising, areas rather than serving to simply protect the interests of the genuine innovators for inventions that have really made.

In addition to this tendency to grant broad claims too readily, the applications process itself has also been criticized. It takes too long to resolve the validity of claims during the applications phase, and the process is open to manipulation by inventors who keep unpromising claims pending for years or even decades preventing third parties from having a clear view of the future playing field in those areas the big players see as most likely to be important. The presence of unfeasibly broad claims pending in a given area is often sufficient to scare off potential investors in competitive technology.

The result has been a quiet revolution in the whole process of intellectual property protection at all levels of the system, from the political masters to the patent offices and even the courts ruling on the interpretation of patent law. For example, in Europe we have seen the changes associated with the aptly named "Raising the Bar" initiative. It is easy to dismiss the changes in the rule regarding the filing of divisionals as esoteric, but from 2010 it will be markedly harder to keep applications pending, and inventors will be forced to narrow their applications to tightly defined claims

**KSR v. Teleflex, 550 U.S. 398 (2007), is a decision by the Supreme Court of the United States concerning the issue of obviousness as applied to patent claims.**



Teleflex, Inc. sued KSR International, claiming that one of KSR's products infringed Teleflex's patent on connecting an adjustable vehicle control pedal to an electronic throttle control. KSR argued that the combination of the two elements was obvious, and the claim was therefore not patentable. The district court ruled in favor of KSR, but the Court of Appeals for the Federal Circuit reversed in January 2005.

On April 30, 2007, the Supreme Court unanimously reversed the judgment of the Federal Circuit, holding that the disputed claim 4 of the patent was obvious under the requirements of 35 U.S.C. §103 and that in "rejecting the District Court's rulings, the Court of Appeals analyzed the issue in a narrow, rigid manner inconsistent with §103 and our precedents."

A great deal of debate has sprung up in the wake of the decision, particularly over the implications on the concepts of "obvious to try", "person having ordinary skill in the art" and summary judgment.

In *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, No. 05-1631 (Fed. Cir. May 9, 2007), the Federal Circuit began applying the KSR case, holding U.S. Patent 5,813,861 invalid as obvious.

The USPTO Board of Patent Appeals and Interferences (BPAI) is citing KSR in about 60% of its decisions related to obviousness irrespective of whether it affirms a patent examiner's rejection or reverses the rejection. Overall reversal rates have stayed about the same, indicating that KSR has not suddenly made all inventions obvious. The BPAI is emphasizing that examiners must still give strong reasons for their rejections. The USPTO management has backed this up with a memorandum to all technology directors instructing them that when making an obviousness rejection "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed."

*Extracted from Wikipedia*

round their invention quicker and more severely than before. The aim, and to a degree the likely result, of these changes is to allow third parties to know much earlier where the “free space” around and between inventions really lies.

In the strategically pivotal US jurisdiction, the political will is fixed on reducing the number and breadth of granted technology patents. A number of recent judgments have strengthened the hand of examiners in rejecting broad (and sometimes not-so-broad) claims, including *KSR v Teleflex* 550 U.S. 398 (2007), a judgment of the US Supreme Court relating to a disputed patent claim for an electronic throttle control. At the heart of the judgment is a new interpretation of 35 U.S.C. §103 relating to obviousness. In essence, the ruling suggests that many combinations of what was previously known are obvious, and therefore unpatentable. This in turn has led to a dramatic increase in examiners at the USPTO throwing out applications that might previously have been allowed, on the basis of sometimes tenuous combinations of the prior art.

If you research life sciences technologies and rely on patents to protect your inventions so that they can attract investment, or if you routinely evaluate technologies for investment that are “protected” by pending applications, and you skimmed over the last paragraph assuming the finer points of specific US Supreme Court judgments were too detailed for you to bother with (all the more so, since it ostensibly related to automotive engineering), then its time for you to talk to specialists in patent strategy. The consequences of the *KSR* judgment are still working through the system, but it is not too doom-laden to suggest that this and not payor pressure or the biotech business model (and certainly not the credit crunch) is the greatest long-term threat to technology investing as we currently know it. Certainly, those who understand it and plan for it have the greatest chance of emerging unscathed a decade from now.

All three of these factors discussed to date have something in common: they all favour survival of the fittest, and promote a leaner model with fewer, carefully selected opportunities being developed. If you invent, or invest in, a technology which is genuinely new, exciting, scientifically sound and offers real patient benefits then you will likely be as successful as you have always been. If, on the other hand, you seek to peddle inferior science dressed up for the ball, swathed in smoke and mirrors, which offers only incremental patient benefit and poor value for money (and we all know there have been plenty of these “golden herrings” sold for substantial sums in the last two decades) then these changes will put you out of business for good.

The fourth factor, however, is rather different and while on the face of it is sensible and well-meaning, it actually benefits no-one: a tighter regulatory environment. As with the patent landscape, the tectonic plates are still moving, and it is not clear where the new equilibrium will eventually lie. In the shorter term, the Obama White House has pushed the FDA towards a still more conservative approach, and the word on the ground is that, as far as the details are concerned, things that were allowable 12 months ago are now triggering resistance from the Agency.

But this short-term trend is only part of a multi-decadal shift towards increasing regulation, and a higher and higher bar to get over in terms of safety and, increasingly, efficacy. On the face of it, such regulation is intended to protect the user (all of us, that is), and it would seem to be self-serving for the drugs industry to call for lighter touch regulation. ‘How can more stringent safety testing possibly be bad?’ cries public opinion.

**“For some, perhaps even the majority, a radical change in approach is going to be required”**

The answer, of course, is the hidden cost of complying with the regulations, both in terms of cash cost for additional studies, but also in terms of otherwise promising new drugs for unmet medical needs which are abandoned

because of equivocal data in a particular, often imperfectly predictive, safety testing regimen. These losses add to the attrition rate that weighs down biotech investment returns.

In addition, ever increasingly vigilant post-marketing surveillance can identify rare but dangerous side-effects associated with a particular product or use. Identifying these issues can only be good, as improved knowledge can drive improved use of available medications. But the current system, which leaves financial liability with drug developers even when the particular side-effect was so rare or so unusual it could never have been predicted during the state-sponsored regulatory pathway, can result in ruin for a developer who has done everything required of them diligently and honestly and delivered a drug whose benefit far outweighs its risks. This has to change. Not, of course, by relaxing our vigil for drug-induced harm but by agreeing a new contract between private enterprise and the state where, in return for diligently following the regulatory guidelines and disclosing all data (a situation we are moving towards but have certainly not yet reached), the state assumes post-marketing liability. It will be enough penalty to the developer that if sufficiently severe side-effects emerge that the market for their product will evaporate, without also facing the prospect of lengthy litigation with their supposed victims leaving the guillotine of unlimited financial liability (particularly in the US) hanging over them.

In the end, regulation that is too onerous, which seeks to eliminate all risk from pharmaceutical use, will drive the development of new drugs to zero. Even the current position, one could argue, is harming rather than improving public health by restricting the flow of new medicines in order to, at least theoretically, reduce the risk of any harm to even a single individual. Until we “grow out of” the current democratic vogue of ‘government by tabloid headlines’ where policy is irrationally modified in response to rare but catastrophic events, while giving insufficient weight to the smaller but still important benefits gained by millions of others (or at the very least underestimating the hidden costs of increased regulatory burden), then there is little hope for reversing the decade-long decline in new drug registrations.

If new drug registrations continue to decline, we are all losers. Not just the biotech sector (which would become a historical quirk), but all of us who rely on pharmaceuticals for a longer, healthier life. Ultimately, even the inventors and investors behind really good products will be forced into submission. Heavier regulation takes survival of the fittest to the irrational limit, where none are fit enough to survive.

So if times are hard at present, in large part due to low capital availability, then my glimpse through the crystal ball suggests that things will get harder still, even as the credit crunch eases. For the best prepared, like all seismic transformations, this will be an opportunity rather than a threat as the chaff is blown away revealing the wheat in all its splendour. But for some, maybe even the majority, a radical change in approach is going to be required – after all, wheat and chaff share a common origin in the ear of corn, and there is still time to influence where you end up.

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