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Schrödinger's Pipeline and the Outsourcing of Pharmaceutical Innovation

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Abstract

In the wake of the Global Financial Crisis (2007-2008) cheaper, softer money flooded the worldwide markets. Faced with historically low capital costs, the pharmaceutical industry chose to pay down debt through share buy-backs rather than invest in R&D. Instead, the industry explored new R&D models for open innovation: models such as open-sourcing, crowd-sourcing, public-private partnerships, innovation centres, Science Parks, and the wholesale outsourcing of pharmaceutical R&D. However, economic Greater Fool Theory suggests that outsourcing R&D was never likely to increase innovation. Ten years on, the period of cheaper and softer money is coming to an end. So how are things looking? And what happens next?

30-Sep-19

Outsourcing Innovation

We Outsourced R&D

In recent years, pharmaceutical companies have turned to external sources of innovation to fuel their depleted R&D pipelines. Driven by the perceived failure of Big Pharma to deliver innovative new products, this search included new models for open innovation: models such as open-sourcing, crowd-sourcing, public-private partnerships, innovation centres, Science Parks, and the wholesale outsourcing of pharmaceutical R&D (1) (2). With their lower cost base, these new players – more entrepreneurial, less risk-averse than the established players – promised a new era of cheaper, more efficient, more innovative R&D.

We are now ten years into the virtualization of pharmaceutical research and development. The recent IQVIA Report (3) on *The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch* highlights the increasing role of smaller emerging bio-pharma companies in the R&D supply chain (4). So, how well are we doing? Are we really seeing the expected rise in innovation? Will the hoped-for improvements in R&D productivity sufficient to secure future earnings? And, what happens next?

Follow the Money

Do Big Investors Believe in Big Pharma?

While there is still optimism in some corners, the early signs are not great. R&D productivity continues to decline, investors have seen a continued fall in returns on their investments, and we have seen a notable slow-down in annual growth especially in Europe and Japan (5) (6) (7) (8). The industry may not be in a complete state of terminal decline; the more optimistic point out that current profits have always been more likely to be derived from mainly older products (3) (7). However, despite its proponents, the big investors seem unconvinced that Big Pharma, with its largely outsourced model of innovation, offers the prospect of significant future returns.

Investors currently favour other technologies over pharmaceuticals. Apple, Alphabet, Microsoft, Amazon and Facebook are collectively worth $3.3 trillion – more than three times the collective worth of the Top 21 Pharmaceutical Companies (9). Right now, we have a company that streams music that is far more valuable than any pharmaceutical company. This suggests that the markets, for one, are not massively optimistic about the prospective returns from the outsourcing of pharmaceutical R&D. So, what is going on?

30-Sep-19

The Global Financial Crisis

The Rise of Cheap and Soft Money

Innovation through the development of new drugs and treatments is key to the return of capital to owners and investors in Big Pharma. However, the ability of R&D to innovate can only be funded by current profits, retained profits, or new investors. This leads to tension. Managing the trade-off between a) returning capital to owners and investors as a reward for their investment, and b) securing future earnings through R&D is a critical requirement for long-term market success.

The Global Financial Crisis (GFC) of 2007–2008 led to a fall in interest rates. The cost of borrowing went down. Fearing economic stagnation, the central banks released money into the economy. By 2016, the central banks of the United States, Japan, Europe and the UK had created over $9 trillion of money. The economic decline post-GFC meant an increase in the availability of **cheap** money (at a lower interest rate – see **Box 1**).

Faced with historically low capital costs following the GFC, the pharmaceutical industry had the option to use this cheap money to invest in future returns through increased R&D spending. Instead, they chose to pay down existing debt by buying back shares. In 2017 alone, 13 of those Top 21 Pharmaceutical Companies returned over $50 billion to their shareholders in the form of share buy backs (9). Of course, buying back shares also reduces cash holdings – helping to ward off hedge funds and asset strippers for example – but using cheap money to return capital to shareholders has been a systemic feature of the last ten years (10).

In addition, the GFC meant an influx of soft money – where **risk** is priced lower. Fearing economic stagnation, governments made more money available through seeding initiatives, innovation grants, and support to smaller, entrepreneurial start-ups. With capital from the shadow-banking sector, this cheaper, softer money found its way to outsourced innovators. The economic pendulum was already swinging away from investing in R&D to outsourcing R&D and acquisitions. Ostensibly, there was a good, sound rationale for this. Big Pharma was seen as poor at innovation. At the same time, entrepreneurs saw the availability of funds increase and the costs of those funds fell.

So, what about these smaller, more entrepreneurial players, how have they fared? This is where the new innovation is meant to come from? Isn't it? Will the availability of cheap money from the banks and soft money to support small start-ups from government, together with more measured pharmaceutical investment in the Science Parks, come good? Are we about to see the spectacular innovations needed to fuel the Big Pharma pipelines?

The smart money suggests not. There have been a number of high profile success stories – small start-ups that became 'unicorns', privately held companies worth more than US$1B. There are other start-ups, acquired by large pharmaceutical companies with massive rewards to the founders and investors. But the truth is on the whole more prosaic. Most start-ups fail: turkeys rather than unicorns. And, in contrast with smart money, softer, cheaper money distorts the markets, permitting smaller start-ups to continue failing for longer. So, what to do?

INSERT BOX 1

Open the Box

Progression Bias Kills Innovation

Drug development is essentially a highly stochastic process (11) (12). Essentially, in R&D, we ship boxes along the development pipeline. Each box may, or may not, contain a marketable product. At each stage in the development process, we either bin the box or pass it down the line. As we move through the development process, the conditional probability that our box contains a marketable drug may increase. In early development, there may be a 5% chance that our drug will pass all of the hurdles and make it to market. By Phase 2 the probability that our box contains a marketable drug may have increased to, say, a 50% chance. But, like Schrödinger's cat, it is not until we actually open the box at the end of the process that we know for sure whether the contents of our box are alive or dead. Without marketing authorization approval, our drug is dead.

INSERT BOX 2

The problem with stochastic processes is that they behave in unexpected ways. A good example is the Development Speed Paradox (13). This is the observation that increasing development speed by reducing the cycle time of successful molecules may INCREASE the expected time to first marketing authorization approval (see **Box 2**). Conversely, building opportunities to fail unmarketable molecules earlier in the development process – 'fast-fail' or 'quick-kill' strategies – will shorten the time to first marketing authorization approval (11) (12) (14).

How does this arise?

With high-risk, stochastic processes such as drug development, the key to increased productivity is to terminate failing projects quickly in order to free up the pipeline to evaluate more viable targets (11) (14). When development resources are constrained, failing compounds rapidly clog the pipeline, preventing the evaluation of perfectly viable products. By focusing on the small minority of molecules that make it to market, the development speed initiatives of the 90s saw R&D productivity fall at a time when drug development cycle times halved (13). The effect was to reduce pharmaceutical R&D productivity. The pipeline becomes choked with dead and dying cats. The solution is to kill failing projects quickly (15). This sounds bad – failure has such negative connotations – but killing failing projects means we avoid incurring the opportunity costs of progression bias (14). And progression bias – the reluctance to terminate failing projects quickly – is at the heart of the problem (16).

Large pharmaceutical companies are notoriously bad at terminating failing projects (16). Ironically, this made the outsourcing of pharmaceutical R&D an attractive proposition. Recognizing that their in-house programmes were prone to progression bias, R&D was outsourced in the belief that other companies would be better at making those decisions. It is a good, sound rationale for the outsourcing of pharmaceutical innovation. It has just one tiny little problem. That's not how economics works.

30-Sep-19

Shark Tank

Greater Fools and Ruthless Rules

The reality TV program 'Shark Tank' – 'Dragon's Den' in the EU, or 'Tigers of Money' in Japan – allows entrepreneurs to pitch business ideas to potential investors. The entrepreneurs make business presentations to a panel of five investors – the 'sharks', 'dragons' or 'tigers' of the title - who decide whether to invest in the company. The sharks often find weaknesses and faults in an entrepreneur's concept, product, or business model. The entrepreneur can make a handshake deal on the show if a panel member is interested. However, the entrepreneur may be savaged during question time. And if all of the panel members opt out, the entrepreneur leaves empty-handed. While the sharks are paid as cast stars of the show, the money they invest is their own money. The sharks are experienced investors, their risk assessments sound, and their valuations of that risk accurate. Our sharks are ruthless. Accordingly, their investments are good, sound, rational investments accurately reflecting the risks and likely value of the proposed business.

However, in reality, investments do not need to accurately reflect risk and value in order to be considered rational.

In economics, Greater Fool Theory states that the price of an object is determined not by its intrinsic value, but rather by the, possibly irrational, beliefs and expectations of market participants (17). Thus a price can be justified by a rational buyer under the belief that another party is willing to pay an even higher price. In other words, one may pay a price that seems "foolishly" high because, quite rationally, one may have the expectation that the item can be resold to a "greater fool" later. Unfortunately, the search for a "greater fool" creates a culture where progression bias is more, rather than less, likely.

In drug development, our goal should be to terminate failing projects as quickly as possible. Outsourcing innovation to smaller players – with the intent of acquiring the more successful ones – was seen as a way to sort the wheat from the chaff. However, with few drugs, or in some cases a single drug, progression bias is likely to be stronger in smaller start-ups (18). Often, for start-ups, venture capitalists and the shadow banks that made initial investments, the ultimate goal is to sell the start-up. In the search for a Greater Fool, a rational strategy for the seller is to downplay the risks, and overestimate the value. As a result, the strategic objectives of small start-ups and Big Pharma may not be fully aligned.

So, as the era of cheaper money and softer money comes to an end, who will be the survivors and who will fall by the wayside?

What Next?

'New Wave' Mergers and Acquisitions

The evidence to support improved R&D productivity through outsourcing to smaller, more agile start-ups is still rather weak. If outsourcing innovation has relied on softer, cheaper money that does not reflect the true risks, what happens when the money dries up? The threat to global R&D may be significant – see Figure 1. And the nature of global capital structures means that this would likely be felt, at least initially, outside of the USA.

INSERT FIGURE 1

One, perhaps unlikely, response is that we will see no change in behaviour – progression bias and the search for the greater fool will triumph. As sources of cheaper, softer money dry up, the industry enters a period of terminal decline.

Alternatively, Big Pharma might seek to realign the goals of the smaller players with those of Big Pharma. This may require longer-term relationships with those smaller R&D innovators. The key will be to establish effective management systems permitting those innovators to continue to do what they do best without carrying too much corporate ballast. For Big Pharma, learning to live with cultural diversity may be critical to longer-term survival.

In addition, there may be a rebound effect with Big Pharma seeking to bring R&D back "into the tent". Internal R&D investment can only take place at the cost of returning less funds to investors. This may depress the value of some companies, triggering a new round of acquisitions and mergers among the bigger players. Those leading the changes will need to consider carefully whether the need for cultural alignment across the organization merits the threat it presents to innovators and innovative thinking. Old fashioned, cultural alignment, or "corporate homogenization" initiatives characteristic of previous mega-mergers are unlikely to work. Instead we are likely to witness a round of less aggressive, or 'New Wave', mergers and acquisitions supporting innovative cultural diversity, characterized by a minimum of cultural disruption.

As the tide of softer, cheaper money recedes and the under-pricing of risk in R&D comes to an end, the pressures to reduce progression bias will increase. The future may still be promising for those survivors who manage their internal and external discovery pipelines well: those with a light touch who have learned to terminate failing projects quickly.

Conclusions

The Future is Interesting

The outsourcing of pharmaceutical innovation - open-sourcing, crowd-sourcing, public-private partnerships, innovation centres, Science Parks - was positioned as a response to the perceived failure of pharmaceutical research and development to innovate and improve R&D productivity. It was facilitated by the sudden availability of softer, cheaper money from banks, governments and institutions under-pricing R&D risk following the Great Financial Crisis of 2007-2008. There have been a number of high profile success stories – those fabled unicorns capitalizing upon increased investment from these sources. Ten years on, the pendulum is set to swing. The winners will be those who have learned to eliminate progression bias. Those who have learned to re-frame project termination as prospective future gains. Those bringing 'Shark Tank' economics to Pharmaceutical R&D.

Figure Legend

Figure 1: The Impact of the Global Financial Crisis of 2007-2008 on the Pharmaceutical R&D Innovation Landscape. Historically low interest rates meant that cheap money and soft money flooded the market. Rather than use low interest rates to invest in in-house R&D, pharmaceutical companies sought to reduce debt and buy back shares. At the same time, cheap money and soft money permitted the growth of outsourced innovation. Unfortunately, progression bias is likely to be higher in these smaller companies. Without 'shark tank' economics, the price is likely to be further reductions in R&D productivity.

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Box 1: The Development Speed Paradox

Intuitively, we might expect that the time taken to complete a task decreases as development speed increases. However, for stochastic processes, the *Development Speed Paradox* states that the expected time to complete a task may actually **increase** as development speed increases, **reducing** R&D productivity.

How on earth does this paradox arise?

Say we have two tasks (A and B) to be completed in series where B is only performed if A is successful. Let the probability that A is successful be p, the time taken to complete A be T_a, and the time to complete B be T_b. Then the expected time (ET) for both A and B to be completed is given by:

$$ET = (1/p)\, T_a + T_b$$

Say that with the current system it takes two years to complete Task A, and a further three years to complete Task B. This gives a cycle time for successful molecules of 2 + 3= 5 years. This is Scheme 1.

Say that we are looking to redesign the process. Let's say that by gathering an additional six months data during Task A, we halve the time taken to complete Task B from 3 years to just 18 months. This gives a cycle time for a successful molecule of just 2.5 + 1.5 = 4 years. This is Scheme 2.

On the face of it, the new process (Scheme 2) looks rather attractive. It has a shorter cycle time than the old-fashioned process (Scheme 1) and adding six months to Task A allows us to halve Task B.

However, if the probability that Task A is a success is low, say 10% (p= 0.10), then the expected time to complete both tasks:

$(1/_{0.10})2 + 3 = 23$ years — Scheme 1

$(1/_{0.10})2.5 + 1.5 = 26.5$ years — Scheme 2

The cycle time may be longer for Scheme 1, but the expected time to complete both tasks successfully is actually shorter for the old fashioned process. Our new process, Scheme 2, makes things worse. So it is that cycle time reduction, while increasing development speed may actually increase the time to first marketing authorization.

For a more complete treatment - see **Lendrem DW, Lendrem, BC.** 2014 *The Development Speed Paradox,* Drug Discovery Today, Vol. 19, pp. 209-214.

Box 2: Glossary of Terms

Cheap money – *money available as loans at low interest rates.*

Soft money – *money where risk is priced lower, such as grants or other development loans to support businesses from institutions underpricing risk - typically governments seeking to promote economic growth.*

Smart money – *money from experienced investors with a realistic understanding of risks and prospects. See also* **Shark**.

Unicorn – *a small business that goes on to become a huge commercial success.*

Frog – *a small, but not necessarily sound, business seeking a wealthy investor.*

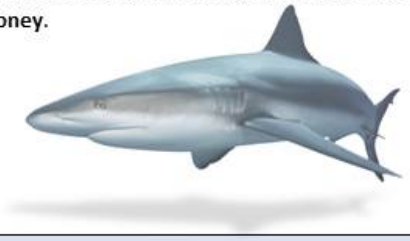
Prince/Princess – *a wealthy, possibly naive, investor in small businesses.*

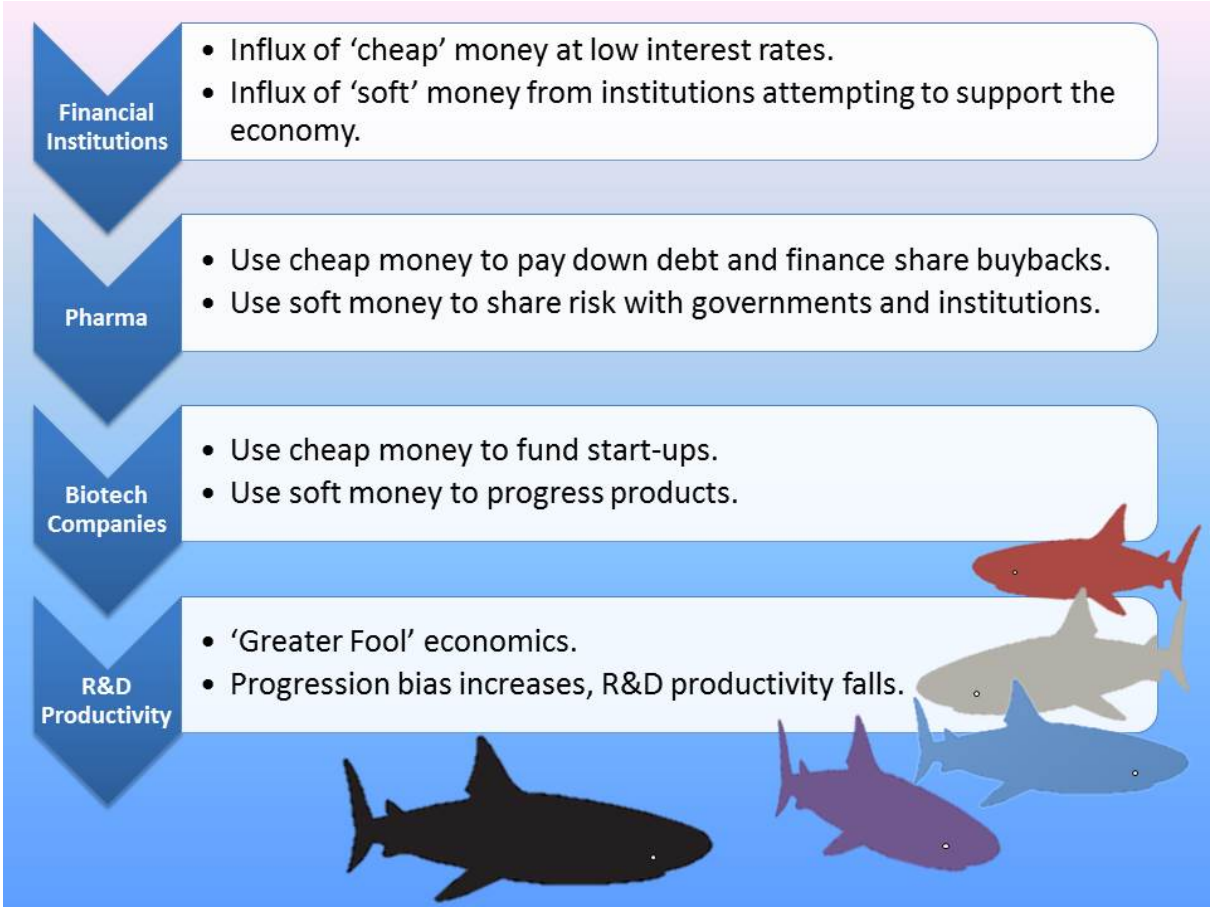
Kissing Frogs – *the action of an organization or government agency making small investments in many businesses in the hope that some become successful.*

Turkey – *an investment that gobbles up resources while awaiting termination. (Named after the flightless bird).*

Fool – *an investor holding irrational beliefs and unrealistic expectations of the market.*

Shark – *a shrewd, or worldly, investor likely to spot flaws quickly in a prospective investment. The holders of* **smart money**.




Financial Institutions
• Influx of 'cheap' money at low interest rates.
• Influx of 'soft' money from institutions attempting to support the economy.
Pharma
• Use cheap money to pay down debt and finance share buybacks.
• Use soft money to share risk with governments and institutions.
Biotech Companies
• Use cheap money to fund start-ups.
• Use soft money to progress products.
R&D Productivity
• 'Greater Fool' economics.
• Progression bias increases, R&D productivity falls.