Defragmenting R&D: Lessons from the Pioneers

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Effective Research and Development (R&D) is the lifeblood of the pharmaceutical industry. The funding of this highly risky and long-term activity had until the last decade or so been primarily left to well-capitalised and integrated global Big Pharma companies. A more recent era of cheap money has now changed all that. Since the market crash of 2008, a combination of ultra-low global interest rates and quantitative easing have changed how pharma R&D is funded, which has in turn changed how R&D is done. Products that take many years to research and develop are now passing through the hands of a multiple and fragmented set of investors, companies and individuals. Yet the complexity of today's R&D requires an integration of many skills, perspectives and experiences. In this paper we explore how a new breed of leading pharmaceutical companies have been responding to the new funding environment, by defragmenting R&D to the benefit of the patients they develop medicines for and the investors that fund their businesses.

From 'Big Pharma does all the R&D' to a highly fragmented R&D ecosystem

Over the last 50 years the pharmaceutical industry has created tremendous value for both patients and investors. In the 1970s to 1990s, all that was required for a pharma company to become a success was the creation

of a single revolutionary product. The rewards for such products were substantial: a combination of patent laws and tight regulation led to an environment where a single product could command annual revenues of $10bn+ with enviable gross margins in the 80-90%+ range. Faced with the prospect of sustained and substantial cash flows from such products, pharma companies typically felt that spending 15-20% of that revenue every year on R&D was a reasonable sum to put aside to create the next product. Investors typically complied – after all the profits and dividends were great, and management had demonstrated success before.

Yet even after investing a substantial chunk of free cash flow in R&D, the cash kept coming in, so pharma companies turned to additional ways to spend their investors' money, more often than not M&A. The consolidation of the industry in the late 20th Century is well documented: companies like today's GSK are the result of a series of M&A activities involving previously successful and integrated companies like Glaxo, Allen & Hanburys, Burroughs Wellcome, Affymax, SmithKline & French, and the Beecham Group. Almost all of todays' Big Pharmas have followed the same path.

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The combination of substantial profits and M&A activity inevitably led to a hangover. Big Pharmas became too big and too comfortable. R&D was seen as a necessary P&L expense, but somehow it wasn't delivering the next great product fast enough to replace the previous one on patent expiry. Eventually investors in Big Pharma and market analysts started to complain. To cap it all Morgan Stanley urged pharma to "Exit Research and Create Value" in 2010, and the days of large R&D campuses and a substantial and relatively unquestioned evergreen funding of Big Pharma R&D were over.

As with many investor-led adjustments to industries, the solution to complacency was brutal, as waves of cost cutting and R&D site closures swept the industry. A huge diaspora of ex-Big Pharma R&D scientists and executives found new homes in a combination of service companies and a plethora of small and nimble "biotech" companies. The industry therefore fragmented: Big Pharma acknowledged that "outside" was sometimes better than "inside". New and rapidly growing service companies filled the gap left by pharma companies, first in clinical trial execution, then earlier in the value chain into discovery, and finally towards fully integrated R&D services. And they found willing customers in the virtual and flexible biotechs funded by Venture investors to advance assets to a point where they could be sold to their former colleagues in Big Pharma.

Cheap money has reinforced R&D fragmentation

The restructuring and fragmenting of the pharma industry into small biotechs, Big Pharma, and multiple Contract Research Organisations (CROs) seeded a very different R&D landscape to the previous era of integrated and mid-sized pharma companies that created the successes and wealth that then led to Big Pharma consolidation.

The ultra-low interest rate era since 2008 has in turn now created and cemented an investor environment that encourages and reinforces industry fragmentation. Today's "cheap money" era has led to an increasingly diverse set of methods for institutional investors to put capital to work in the pharmaceutical industry. At the highest level, depending on their various appetites for risk, institutions can invest in:

- **Private Equity funds (rapid profit growth) which in turn take stakes in:**
  - Lower-risk often mid-sized pharmaceutical companies with relatively established product ranges, little R&D and reasonably reliable cash flows Service companies and CROs with reliable cash flows from contracts with a diverse range of pharma/biotech companies

- **Venture Capital funds (high-risk, high-return) which in turn invest in:**
  - Small and virtual biotech companies with promising assets that require a few years of funding to reach a point where they can be sold to pharma companies
  - Platform discovery biotechs with a unique technology that can create multiple assets of interest to pharma companies

- **Hedge funds (medium-risk, medium-return):**
  - Take advantage of risk asymmetries in the market
  - Take stakes in private and listed pharma/biotech companies

- **Stock-market listed companies (stable returns and/or upside):**
  - Big Pharma with sustainable and reliable income streams with good prospects for dividends
  - Early but more established biotech companies with potential for massive value increase on success of their products
  - Mid-cap pharma/biotech companies with sustainable prospects from a mix of own and partnered products

- **Privately held companies (medium risk and return):**
  - Small to mid-sized companies that choose to invest for the long-term development and commercialisation of niche products

The flow of money into these asset classes is undoubtedly shaping the way R&D is both funded and executed. For example a resurgence of Venture Capital investing in pharma/biotech over the last decade has driven the creation of small and virtual companies that fit the model of delivering a potential exit for investors in 3-5 years. Meanwhile Private Equity funds have

seen the pharmaceutical services sector as an interesting way to generate reliable and growing profit streams from pharma/biotech companies that do not like investing in fixed costs. The small biotech and service sectors are therefore both here to stay while investors are seeking the type of higher returns that the era of cheap money demands.

Fragmentation has increased the price and risk of external R&D

In a sense the newly fragmented world of eager and nimble small biotechs producing innovative products to be bought at huge prices by Big Pharmas that need to replenish their R&D pipelines is a repeat of history: profitable Big Pharmas are now spending their excess cash on the external hope that a nimble biotech will provide them with their next product rather than the old internal hope that their own R&D organisations will deliver. And while frothy stock markets allow them to pay inflated prices, this will continue. For recent examples we need look no further than Pfizer's acquisition of Medivation for 40% more than any other pharma company was prepared to pay after a series of negotiations, or Allergan's acquisition of Tobira for an up-front of nearly 500% of its previous day closing share price. Cheap money has therefore created a world of inflated external R&D expenditure. Pharma companies are under constant pressure to increase profitability, so are looking to reduce the internal R&D expense that hits their P&L accounts every quarter. At the same time they need innovation, so are taking on external expenditure on assets and companies that can be charged to their Balance Sheets without any effect on EBITDA. The prices of external assets rose to match such demand.

Correspondingly Venture Capital companies have been eager to invest their Limited Partners' enthusiasm for higher returns in companies that can subsequently be bought at these inflated prices. By contrast family and foundation held companies are unable to keep up with paying these kinds of prices for external innovation. And the sheer volume of external opportunities that are now available for in-licensing or acquisition (many more hope than reality) is creating a real problem for companies trying to sort the wheat from the chaff.

Whether the inflation in asset prices caused by the double dynamics of Big Pharma internal cost cutting and venture funds' appetites for creating small companies that can be bought has peaked yet or not, one thing is for sure: Pharma R&D is too long-term and risky an endeavour to leave solely to the short-term volatility of investors' appetites for risky asset classes. So a number of smaller and mid-sized pharma companies are stepping in to carry out the kind of integrated R&D that does not require constant purchasing of external assets and companies.

Pioneering a newly integrated R&D model

A new breed of entrepreneurial R&D integrators are now emerging to challenge the dogma of "fragmented is beautiful" that the new funding landscape has created. Such companies recognize the value of continuity and integration of highly diverse skills and understanding from science, medical, commercial, and partnership disciplines among others. They know that in order to buy the right external assets when they need to, they need to be excellent pickers and excellent partners post-deal or the knowledge residing in their partners will be lost.

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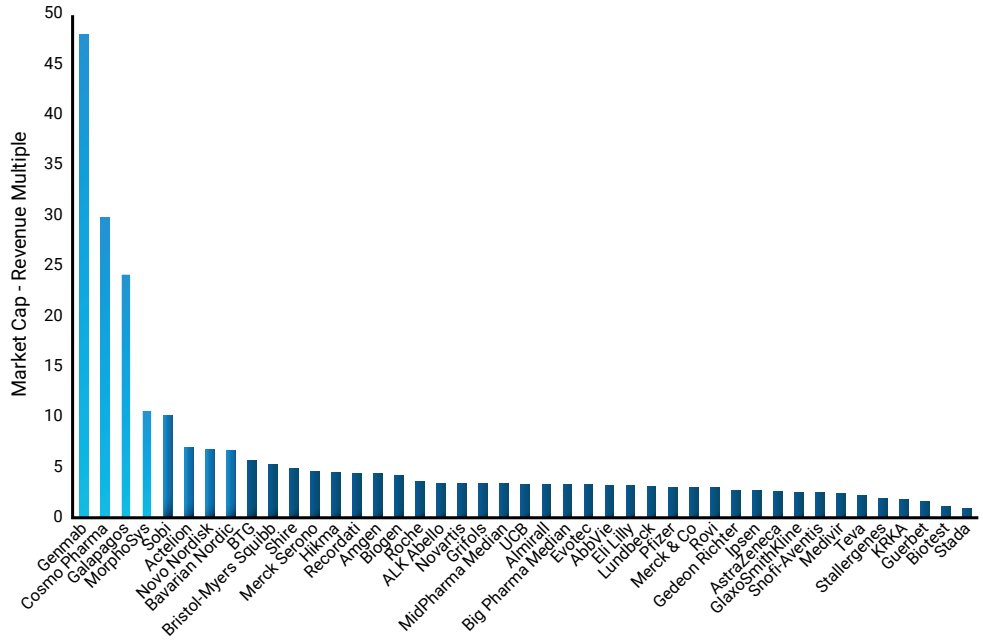
A new generation of integrated mid-cap pharma companies is out-performing Big Pharma



Note: For each company market cap was recorded end of Q1 2016; annual revenue is as stated from 2015 for all companies

The two common features of all the companies that have higher market cap to revenue multiples are focus and integration. For focus, some "Platform Pharmas" choose a technology platform that provides multiple shots on goal through own-development or partnerships, and other "Specialist Pharmas" choose a particular disease area, usually associated with intimate knowledge of the science and medical elements of the disease and strong connections with relevant physicians and patients. For integration, all companies have retained internal capability from discovery through to late stage development, with most already in commercialisation and the others very close.

1. Platform Pharmas (Genmab, Cosmo Pharma, Galápagos, MorphoSys)

Genmab, with it's impressive 48X market cap-revenue multiple (compared to a MidPharma average of 3X), is a Danish company that was founded in 1999 to develop and commercialise a portfolio of human antibodies. Genmab now has two on-market products, ofatumumab and daratumumab, and multiple proprietary technology platforms for antibody production. Genmab's antibody expertise and technology platforms are expected to provide a stream of future product candidates – the likely reason for Genmab's high value.

We had comparable findings in Cosmo Pharma (30X multiple), Galápagos (24X multiple) and MorphoSys (11X multiple). MorphoSys is similar to Genmab in terms of its antibody focus, owning the rights to several proprietary techniques for human antibody production. Cosmo Pharma has a proprietary MMX technology platform for gastroenterology drug delivery. Galápagos is a bit different – it has a proprietary discovery machine that makes use of patients' cells to discover new drug targets, meaning its ability to convert disease targets into therapeutics is its value driver. Its business model is less about straight out-licensing its technology, and revolves more around working with larger MidPharmas and Big Pharma partners to obtain patient expertise and provide access to its proprietary discovery system.

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Remarkably, in the span of 2009 to 2015, none of these company's revenues has grown by more than 15% CAGR – good, but not spectacular. This goes to show that the value assigned to these companies is undoubtedly based on future potential, and not past performance. Additionally, this suggests that these 'Platform pharmas' are focusing more on long-term growth, and their investors are not necessarily seeking quick wins from single product bets.

2. Specialist Pharmas (Sobi, Actelion, Novo Nordisk, Bavarian Nordic)

The second group of pharma companies identified through this analysis is made up of Sobi, Actelion, Novo Nordisk and Bavarian Nordic, having market cap-revenue multiples ranging from 7X (Bavarian Nordic) to 10X (Sobi). The interesting trend that we see here is that all of these companies have focus: they are choosing to build a dominant presence in a specific domain. Sobi focuses exclusively on rare diseases. Actelion recently started emphasising rare diseases with its small molecule platform, supported by continuing life cycle management of its pulmonary arterial hypertension franchise. Novo Nordisk is synonymous with diabetes and, to a lesser extent, haemostasis and hormone therapy. Bavarian Nordic focuses on immuno-oncology and infectious diseases, which may not seem similar upon first glance but which share an underlying virus-based technology platform.

Defragmenting R&D creates value

While the market cap to revenue multiple is only one (relatively crude) measure of R&D success, our experience from both privately held and publicly listed companies is that there is real value from a continuity of knowledge and perspective that comes from being integrated in R&D. However the nature of the integration, between new functions and disciplines, is fundamentally different to where Big Pharma was decades ago. Rather than creating huge internal R&D machines, strong innovators now seamlessly integrate R&D, commercial and Business Development (BD) perspectives throughout the value chain. Through this, they can pick the best assets to bring in and develop them in a way that matches ever-changing commercial realities.

The challenge is that the new integration practised by the pioneers requires a very different culture from the old integration that created success for pharma companies in the past. Old habits die hard, and many pharma companies are wrestling with a legacy of highly functional and specialist skill-focused R&D organisations that do not have the culture or mindset of the modern integrators: New habits such as relentless external wiring, seamless joint working with BD and commercial colleagues, fast decision-making and capital discipline do not come naturally to traditionally siloed R&D organisations.

The good news is that leading pharma companies are now restructuring their R&D organisations to suit the new fragmented reality of a plethora of small biotechs and plenty of strong R&D service organisations that has resulted from the era of cheap money. These defragmenting pioneers are creating organisational and governance forms that instil dynamism into

those that are responsible for innovating (typically through smaller multi-discipline project/portfolio teams or units) and instil operational excellence into those that are responsible for delivering output on time to high quality, such as clinical operations, where there are clear options to outsource and get the benefits of external experience and capabilities.

Since looking outside for pipeline replenishment is likely to remain expensive and risky while global money is cheap, pharma companies must re-invent their R&D organisations in ways that they can genuinely innovate and execute. This requires a mix of clever partnering skill, profound multi-disciplinary knowledge, and operational excellence to deliver the right project results with the efficiency and quality required to bring great products to market.