HEALTH CARE: THE EMERGENCE OF A NEW PARADIGM

The last decade has been a decade of transformation for the Health Care sector: from being considered the “sick” sector for some time in the 2000s and chronically underperforming over the period, with low R&D productivity, the prospect of the extended “patent cliff” period and the associated losses in top line revenue, and the continued growth of generics and the biotechnology industry, to emerging as the second best performing sector globally in the last few years.

EMBRACING MODULARIZATION AND OUTSOURCING

Biopharmaceutical companies have had to adapt and evolve in how they do both R&D and manufacturing. The sector had been making extensive use of outsourcing of R&D, facilitating the emergence of a significant CRO industry, and embracing alliances and partnerships with academia, as well as M&A as a means to replenish R&D pipeline and boost drug approval numbers. On the manufacturing side, cost savings have been possible through use of CDMO providers.

THE FUTURE REMAINS BRIGHT DESPITE HEADWINDS

More short-term adjustments are required with the re-introduction of trade tariffs by the US and China, and the pricing pressures both in the US, the biggest drugs market globally, but also elsewhere. However, the secular trends of aging global population, the rise in incidence of chronic disease, as well as the emergence of a consumer-centric approach to how health care is delivered through digital tools and connected care, are all going to be factors supporting the long-term growth of the Health Care sector.
This AQ focuses on the significant shifts the Health Care sector has experienced in the last decade, particularly affecting the product-focused industries such as pharmaceuticals and biotechnology, as well as the drivers for the development of the sector going forward.
The Health Care sector globally has undergone a quiet revolution in the last decade. Regulatory changes in the US with the introduction of the Affordable Care Act by the Obama administration in 2010 on the one hand, with on the other hand continued regulatory adjustments across all Western markets with increased focus on “value” for patients and the ominous “patent cliff” with its ripple effects still working through the sector as we speak, have hit and their effects have been absorbed by the Health Care sector as a whole, for it to emerge as one of the best performing sectors of the last few years globally.

This was accompanied with the M&A deal frenzy of the last few years, in part spurred on by tax changes in the US in the last year, along with the emergence of China as a global player in the Health Care M&A space, and finally technology driven changes in how R&D is conducted, with significant advances in fundamental science.

A decade ago the sector was considered the “sick” sector of the global economy, with innovation on the decline as measure by productivity of R&D dollars, and the decrease in the number of new molecular entities approved by regulators. The sector was facing an uphill struggle to preserve top line revenue with the advent of the “patent cliff”, and has had to evolve and adapt to thrive.

Today, the sector has been transformed, having embraced modularization at most stages of R&D and production, with the use of Contract Research Organizations, M&A, alliances and partnerships across the industry, as well as Contract Development and Manufacturing Organizations. New players, such as Biotech, have grown to represent a significant part of the Health Care sector, transforming the science of medicine making. These elements together have increased the pipeline of R&D across the biopharmaceutical subsector. The regulator in the US has also put increasing focus on a collaborative approach and accelerated pathways to approval, in order to facilitate a rise in the number of active substance authorizations. At the same time, headwinds for the sector remain, with unrelenting threat from generics and biosimilars, the continued government and payers scrutiny on pricing, and regulator attention to preventing anti-competitive practices.

With the looming increases in interest rates which will invariably increase the cost of capital and may further dampen the buoyant Health Care sector, investors may wonder whether valuations in some instances have become significantly stretched and expect a continued pull back on the back of the October and November sell offs. Also, the newly re-introduced trade tariffs between US and China are likely to require supply chain adjustments in the biopharmaceutical subsector, because of its global footprint.

Despite the near-term obstacles, the long-term trends will continue to provide support to the sector, among which the aging global population, the increased incidence of chronic disease across the emerging economies, as well as the introduction of universal health coverage in many countries. The future of the Affordable Care Act in the US is still unclear over the near term, as the current administration has worked to limit its reach. However, it has been doing so to a much lesser extent relative to the harshness of the rhetoric during the 2016 presidential campaign, so there may be hope for the ACA structures to remain with us for the long term.

Finally, the nature of health care itself is also changing with the emergence of integrated care facilitated by the use of technology and digital diagnostics. The increasing focus on the patient as the consumer who is in control of their health and treatments, and the focus on consumer choice has been a central pillar supporting the emergence of the digital health technology sub-sector. This digital health technology stream has enjoyed a strong wave of VC funding and has invited many corporate M&A deals in the last 18 months. The foray of the likes of Amazon into the health care space has created further disruption to the comfortable status quo in the sector.

The health care sector is accustomed to continually adapting and exercising agility to preserve its top line revenues and control costs. It will need to continue using its agility in order to stay competitive.

We look forward to hearing from many of our readers with more insights into and views on the health care sector, and engaging into a debate on its future.

With warm regards from the team,

ANJELIKA KLAMP
Managing Director
HEALTH CARE: THE EMERGENCE OF A NEW PARADIGM

Since the introduction of Obamacare in March 2010 and to end of November 2018 when we write this AQ, the global Health Care sector, whether assessed by its broad or narrow measures, has posted an annualized total rate of return in excess of 13%.

TOP OF THE HEAP SINCE 2010...

Health Care has in fact been the second-best performing sector globally over the period, only narrowly beaten by Information Technology and almost tripling in value since the introduction of the Affordable Care Act in the US in March 2010.

In 2018 year-to-date, despite the strong sell off in US biotechnology stocks in October and November, the overall strong performance of Health Care has continued making it the best performing sector globally, with the MSCI ACWI Health Care posting a YTD gross return of +11.16% against the MSCI ACWI index returning -2.07% as of end of November 2018. The US Health Care sector returned a healthy +14.04% in Q3 2018, making this its best quarter since Q1 2013.

The market for both corporate and PE deals has also been lively in the last couple of years, with companies, supported by the significant reduction in the corporate rate of tax from 35% to 21% introduced by the Trump administration, and the one-off rate of tax of 15.5% on repatriation of foreign cash balances as of end of 2017, as well as zero federal income tax on new foreign earning starting from 2018. The VC market has been equally buoyant with the volumes of deals exceeding historical levels.

Among the large deals in the corporate M&A space, we have seen Celgene acquiring Juno Therapeutics¹ for US$ 9 billion and Impact Biomedicines for US$ 7 billion², as well as Sanofi US acquiring Bioverativ for US$ 11.6 billion³.

The PE deal landscape has continued to flourish maintaining the long-term trend of increasing deal numbers. A few mega deals by private equity firms stood out, such as KKR’s acquisition of Envision Health Care Corporation for US$ 9.9 billion⁴, and Sound Inpatient Physicians Holdings’ divestiture from Fresenius Medical Centre to an investment group run by Summit Partners for US$ 2.15 billion⁵.

It is expected that the number of PE deals in the Health Care space will continue its long-term up-trend, and PwC expect this to increase to potentially 747 deals in 2019 based on Pitchbook data⁶.

6. PwC, Private equity: Healthcare’s new growth accelerator, 2018
In the VC space, in the US alone in the twelve months to end of Q3 2018, a total of US$ 20.9 billion has been invested in a total of 729 Health Care deals. This is a significant uplift from the US$ 13.7 billion invested in US Health Care VCs in the prior 12 months and can be assessed in the wider context of global VC deals in Health Care nearing US$ 28.6 billion over the same period (of which Asia represents US$ 5.2 billion, and the rest is in Europe).

According to PwC and MoneyTree data, it also reflects the increase in mega-rounds, which account for US$ 2.4 billion invested across 12 deals in Q3 2018 in the US alone. Among the larger deals of Q3, there have been the Samumed deal of US$ 438 million and the 23andMe deal of US$ 300 million.

The arena of digital health, which traditionally sits within the tech space, has also been very buoyant with US$ 6.8 billion raised in the first three quarters of 2018, and a total of 82 digital health companies acquired over the same period.

Despite the strong sell off in US biotechnology stocks in October and November, the overall strong performance of Health Care has been maintained in 2018 to date.
...DESPITE THE RECENT SOFTENING

Of course, there have been significant disparities in how the various industries within the broad Health Care sector have performed over the period, with notably the strong sell off in the large US biotech space in the months of October and November this year, erasing gains made by the industry earlier in the year.

Also, the picture in Q4 2018 has somewhat changed with a slowdown in VC activity to around US$ 1.3 billion worth of biopharma deals as of Q4 midpoint. Further, the IPO activity seems to have slowed down in the second half of 2018\(^8\) with some IPOs being postponed and IPO discounts making a return, after a strong IPO market in the first half of the year. Despite this slowdown in venture activity and increased volatility in the large biotechnology space, 2018 remains a bumper year in terms of corporate activity across the Health Care sector, as a whole.

AFFORDABLE CARE ACT: SHIFTING OUT DEMAND CURVE FOR HEALTH CARE

It appears that, since its introduction, the Affordable Care Act of 2010 (ACA) has served as one of the supporting factors to the Health Care sector, by shifting outwards the demand curve for Health Care products and services. The addressable market for Health Care companies has potentially increased by an additional 20+ million US consumers and the US uninsured rate has been reduced from 16% of the population in 2010 to 9.1% of the population\(^9\) or 29.3 million people in 2017.

There are variations in how enrolment in different sections of the ACA have progressed since ACA’s launch. While ACA Medicaid enrolment has been ahead of 2012 estimates, ACA Exchanges enrolment has fallen short of initial expectations and is estimated to be at around 9.7million people in 2018, instead of the 26 million estimated in 2012 by the Congressional Budget Office\(^10\).

7. PwC/CB Insights, Healthcare MoneyTreeTM Report, Q3 2018
8. https://www.leafscience.org/samumed/
Despite this, the total increase in enrolments into Medicaid and the ACA exchanges collectively since baseline year 2013 stands at around 25.3 million people. This is a considerable increase in insurance coverage, which has significantly expanded the addressable market for the Health Care sector companies.

HEALTH CARE: THE "SICK" SECTOR 10 YEARS AGO

However, things were not always as positive for the sector. Thinking back as recently as a decade ago, the prevailing consensus was that the pharmaceutical industry, the largest industry within the Health Care Sector representing around 45% of its market capitalization, was in crisis. It was beleaguered with a lack of R&D productivity, and the looming "patent cliff", due to hit in the following few years. As a result, between 2004 and 2010, MSCI ACWI Health Care Index underperformed the global MSCI ACWI in six years out of seven (with the exception of 2008, when the Health Care Index proved to be more resilient in the midst of the turmoil of the Financial Crisis). In total over the period, the Health Care sector underperformed the global index by a cumulative 23.53%.

THE LOOMING "PATENT CLIFF"

The big pharma companies' reliance on a handful of blockbuster drugs meant that related patent expiries between 2007 and 2017 were expected to result in loss of lifetime sales of US$ 915 billion for the top ten patent losses alone. For an industry with global annual sales of US$ 599 billion back in 2007, this is a significant number by any measure, and was causing anxiety to both the industry and investors alike.

What a difference a decade makes: ten years ago the financial markets wondered whether and how the product side of the sector, with pharma and biotech representing approximately 60% of the Health Care sector market cap, was going to survive the patent cliff.
### 10 Largest Patent Expirations of the Decade

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Year of patent expiry</th>
</tr>
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<tbody>
<tr>
<td>AbbVie</td>
<td>Humira</td>
<td>2007</td>
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<tr>
<td>Pfizer</td>
<td>Lipitor</td>
<td>2011</td>
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<td></td>
<td>Norvasc</td>
<td>2012</td>
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<td>GlaxoSmithKline</td>
<td>Advair</td>
<td>2012</td>
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<td>Sanofi</td>
<td>Lantus</td>
<td>2016</td>
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<td>Johnson &amp; Johnson</td>
<td>Remicade</td>
<td>2016</td>
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<tr>
<td>AstraZeneca</td>
<td>Neulasta</td>
<td>2015</td>
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<tr>
<td>Amgen</td>
<td>Diovan</td>
<td>2016</td>
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</tbody>
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Figure 4: FiercePharma with data from Evaluate, Decade's Top Ten Patent Loses

Among the top ten patent losses of the decade to 2017 figure Pfizer’s top revenue generator Lipitor (cholesterol), AbbVie’s Humira (autoimmune disease) and GlaxoSmithKline’s Advair (asthma). The patent cliff was by no means limited to these top ten names, and in fact between 2012 and 2014 alone, 110 products were expected to lose their patent protection, of which 14 were blockbuster drugs according to Elisabeth Pain.

Also, the “patent cliff” is not a one-off event. Patent expiries continue to happen, affecting a number of top-selling drugs. A second wave of “patent cliff” is about to hit the industry with a cluster of patent expiries due in the next six years. The market research firm EvaluatePharma estimates that between 2018 and 2024, revenues worth US$251 billion per annum are at risk due to patent expiries during the period. The actual loss of annual revenue is projected to be lower at around $139 billion, through mitigation strategies.

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15. MSCI ACWI sector indices, CITE analysis, [https://www.msci.com/documents/10199/8d97d244-4685-4200-a24c-3e2942e3adeb](https://www.msci.com/documents/10199/8d97d244-4685-4200-a24c-3e2942e3adeb)
The ever increasing drug R&D development costs and the decline of drug approvals per R&D dollar were for a long time a conundrum the biopharmaceutical companies needed to solve

A decade ago, the market questioned how the industry was going to remedy the significant revenue losses expected upon patent expiries, with a R&D pipeline at lowest levels in decades, many disappointing clinical trials and particularly costly late stage candidate failures, declining FDA approval rates and an increase in the costs of R&D.

INEFFICIENT R&D

Drug R&D costs, already high in 2008, have continued to climb steadily over the last decade. Estimated at US$1.2 billion in 2010, in 2017 the R&D cost of bringing a New Molecular Entity (NME) to market was assessed by Deloitte to have increased to just under US$2 billion\(^{19}\). Other estimates run by the industry itself (EvaluatePharma) put the average cost of developing an NME as high as US$3.9 billion\(^{20}\). While these estimates vary widely and use differing methodologies, the common theme seems to be that costs have escalated over the last decade due to rising attrition rates in the various stages of discovery over the same period.

Drug development has always been a long and arduous process with low odds of success – it takes on average 12 years to bring a new compound through the development and clinical trials process, and only one in 5,000 compounds discovered at pre-clinical stages eventually gets approved\(^{21}\). For compounds that make it to first-in-man trials stage, their chance of reaching registration was shown to be around 11% in a 2008 study and declined further in the subsequent years.

Further, according to Scannell et al (2012), Moore’s law which is often applied in the realm of electronics to describe their exponential advance, was shown to apply in reverse in the context of pharmaceuticals. In other words, the number of new FDA approved “drugs per billion US dollars of R&D spending [had] halved approximately every 9 years since 1950, in inflation-adjusted terms”, between the 1950s and 2010.

The crisis in R&D productivity is otherwise illustrated by Boston Consulting Group\(^{23}\), where they show that the average returns to R&D since the late 90s had fallen below the long-range WACC, and stood at around 8.5% in 2010 while

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the industry WACC ranged between 8% and 10%. The same BCG report estimated that “90% of industry R&D expenditure [was at the time] devoted to molecules that never reach the market”.

THE EXPLOSION OF BIOTECH

While the pharmaceutical industry grappled with its own productivity crisis, additional headwinds came from the growth of the disruptive Biotechnology industry, which uses different mechanisms for tackling disease targets.

The biotechnology industry, still in its infancy in the 80s and 90s has grown significantly in size in the last fifteen years. According to EvaluatePharma data\textsuperscript{24}, Biologics prescriptions represented 14% of all prescriptions and OTC sales worldwide in 2008. This percentage has today almost doubled to an estimated 27%, and is expected to continue to grow to 31% by 2024. Within the top 100 products sold globally, biologics represented 49% of sales in 2017, which is expected to grow to 52% in 2024.

Today, the biotechnology industry represents approximately 15% of the Health Care sector market capitalization\textsuperscript{25}, and together with the traditional small molecule pharma industry accounts for 60% of the sector. The crisis in R&D productivity also affected the biotechnology industry, with many biologics counting among the drugs with the highest costs of R&D. Further, in the last decade, the continued growth in generics and the more recent emergence of biosimilars have created more disruption for both traditional pharmaceutical companies and biotechnology players. The biopharmaceutical industry had to re-invent itself.

DECLINE IN R&D PRODUCTIVITY IN BIOPHARMACEUTICAL INDUSTRY\textsuperscript{22}

The crisis in R&D productivity in biopharmaceutical industry focused on top-line revenue preservation. To boost R&D pipeline, the industry has re-invented the way it does research by increasing its use of Contract Research Organizations (CROs), fostering partnerships with academia, increasingly using in-licensing agreements, joint ventures and M&A with smaller more specialist firms to increase its R&D output.

External alliances, use of CROs and partnerships with academia has been an important means for the biopharmaceutical industry to boost their R&D productivity. Use of specialist providers for certain tasks from target validation, to lead optimization to animal testing and human clinical trials has been expanding and 80% of biopharmaceutical companies report to use external sources to carry out some of the tasks of their R&D process\textsuperscript{26}.

Various CRO providers occupy specific niches such as combinatorial chemistry, genomics, big data analysis and high-throughput screening, the types of activities that may
require significant upfront investment and time to recruit the right teams. Academic institutions may be particularly suited to helping identify new targets, while other types of organizations focus on conducting work in the early stages of drug discovery and development. In fact, drug discovery represents the largest portion of the CRO market at around 33%, and a significant proportion of the drug pipeline of the 10 largest biopharmaceutical companies originated from outside the company.

Examples of various research outsourcing strategies abound, with academic partnerships including the AstraZeneca’s collaboration with the university of Cambridge, GlaxoSmithKline’s partnership with the University of Leicester, and Sanofi’s collaboration with Harvard, while industry alliances include Actelion’s agreement with Enamine, Pfizer alliances with PPD, ICON and Parexel, as well as Eli Lilly’s and GSK’s partnerships with Parexel.

The CRO industry continues to grow in size at an expected rate of 12% per annum through 2021 to reach US$ 44.4 billion, with IQVIA, LabCorp, ICON, Parexel and PPD among the largest firms.

The use of M&A to add to R&D pipeline has also been extensive, particularly in the last five years, with 2014 and 2015 both standing at over US$ 350 billion in Health Care M&A value, according to a 2018 report by Bain & Company.

2018 has also been a strong year for Health Care M&A, with the first three quarters of 2018 showing a deal value of around US$ 300 billion across global pharma, life sciences and US health services alone, according to PwC numbers.

Among the largest mergers of the last five years are the acquisition of Allergan by Actavis in 2015 for US$ 70.5 billion, the acquisition of Shire by Takeda Pharmaceuticals in 2018 for US$ 81.7 billion and the acquisition of Pharmacyclics by AbbVie in 2015 for US$ 21 billion.

With the benefit of hindsight, not all M&A transactions of the last decade have been viewed as a success by the markets. For example, the consensus is that the Merck and Schering-Plough merger of 2009 did not create any value for Merck, as the Schering pipeline subsequently failed to materialize and Merck’s sales continued to fall for many years post transaction.

Nonetheless, M&A has been one of favoured methods used by biopharmaceutical companies to replenish their R&D pipelines and bring in specialist expertise in strategic areas, to a point where the market questioned whether for larger companies M&A would replace R&D as their core activity.

Other firms, such as Bristol-Myers Squibb, put their focus not only on external collaborations, but also onto tightening their internal governance, and emphasizing cross-functional cooperation to increase their organization effectiveness. This has enabled the company to curtail “progression-seeking behaviour” which attempts to maximize candidate drug progression between various stages of R&D process, in favour of Extensive use of M&A as a means to replenish declining pipelines led investors to question whether M&A was going to replace R&D as the core activity for biopharmaceutical companies.
“truth-seeking behaviour” where teams work together to identify obvious failures sooner along the process. As a result of these efficiency initiatives, its strategic divestitures to rationalize its R&D portfolio, as well as its external alliances with Medarex, Adnexus, Ono and Five Prime for an increased focus on immuno-oncology, Bristol-Myers Squibb has been one of the companies whose financial performance has improved in the more recent years.

...WHICH RESULTED IN AN INCREASE IN PIPELINE AND APPROVALS

R&D has always been a key aspect to revenue generation for the pharmaceutical industry, and the long-term average industry investment into R&D has been in the region of 20% of annual prescription drug sales. Following a dip over the period between 2010 and 2014, the industry R&D spend has picked up again in recent years. This represented R&D investments by the industry worldwide of US$165 billion and an estimated US$172 billion in 2017 and 2018, respectively.

Looking at the total R&D pipeline size historically confirms that there has certainly been a pick up in R&D activity more recently, with the pipeline including 15,267 projects as of 2018, about half of which are in preclinical phases.

How much of this pipeline increase is due to the active management strategies pursued by biopharmaceutical companies over the last decade and how much is through advances in fundamental science facilitated by increased VC and PE funding, is up for debate. One thing which is certain is that the rate of increase in the number of projects has seen a pick up in the last five years.

It is worth noting that the number of companies currently conducting biopharmaceutical R&D has more than doubled from 1,965 in 2008 to 4,134 a decade later. Out of the 4,134 biopharmaceutical companies in existence in 2017, 1,627 have a single product pipeline, and 657 have just two projects.

Also, the rate of turnover in the industry is high, with 670 new companies entering the universe and 487 companies either defunct or exited in the year to January 2017.

Use of external partners, such as Contract Research Organizations, as well as use of buy-and-build strategies has resulted in a pick up in R&D pipeline activity.

Total R&D pipeline size by year, 2001-2018

Figure 7: Pharmaprojects, January 2018

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34. https://www.bcg.com/publications/unlocking-productivity-in-biopharmaceutical-rd—the-key-to-outperforming-
    your
    shaping-portfolio.aspx
The industry remains very fragmented, with a handful of giants with large R&D portfolios, such as Novartis, Johnson & Johnson, AstraZeneca, Roche, GlaxoSmithKline and Pfizer dominating one end of the spectrum, and a long tail of one-drug companies, many of which are financed with VC funding on the other.

An increasing number of research projects are focusing on the same therapeutic areas. For example, while back in 2010 26.8% of the total pipeline was focused on cancer drugs, this number is as high as 34.1% in 2018. However, it is also interesting to note that there has been an increased focus on rare diseases, with around 30% of the 2018 pipeline or 4,615 drugs targeting at least one rare disease. So, while the pipeline has been increasingly concentrated on popular therapeutic areas such as cancer on the one hand, it simultaneously expanded coverage towards traditionally underserved areas.

The breakdown of the R&D pipeline between biologics and traditional drugs stood at 37.9% and 62.1% respectively as of January 2018. The proportion of pipeline represented by biologics is significantly above its long-term average and reflects the increased emphasis on using biologics to tackle new disease targets. However, a logical question to ask would be whether this increase in R&D activity actually results in a higher number of new drug approvals.

At the other end of the funnel, the number of NMEs approved by the US FDA has also been rising in the more recent years, after going through a period of historically low approvals between 2005 and 2010. The dip in approvals in 2016 was compensated by a historically high number of approvals in 2017 with 46 NMEs and innovative biologics approved in that year alone, a level only achieved in 2015 and before that in the 90s. 2018 has seen even more approvals – 55 NMEs have been approved this year so far, a level last matched only in 1996.

Out of the 46 approvals of 2017, 28 were facilitated by the FDA’s increased focus on using expedited development and review pathways, including Fast Track method, Breakthrough Therapy, Priority Review Voucher and Accelerated Approval methods. This has enabled approval of new therapies for rare diseases which affect small populations, and that had in some cases been neglected by the bio-pharma industry for two decades (sickle cell.

The number of new drug approvals has increased, both through changes in corporate R&D strategy, but also through regulators making adjustments to improve efficiency of their review processes.
The number of drugs granted orphan drug status has increased by another 316 in 2018, to bring the total number of orphan drugs to 4,824. FDA has also in the recent years focused on completing approvals within single review cycle, by increasing the amount of dialogue and interaction with applicant firms.

OUTSOURCING AND MODULARIZATION OF MANUFACTURING

To improve profitability, biopharmaceutical companies have also focused on controlling production costs, seeking to optimize production by embracing the use of Contract Manufacturing Organizations (CMOs) and generally modularization.

The emergence of CMOs and the broader CDMO sector date back to the 90s. While initially it was a means for the established pharmaceutical companies to utilize each other’s idle capacity, in the 2000s larger CDMOs, such as Lonza, Patheon and Catalent enabled the explosive growth of the biotech industry by providing scaled manufacturing capacity to small and medium size biotechnology firms. Since 2008, private equity financing has played a role in facilitating the continued growth of the CDMO industry, coming into its own especially with FDA approvals increasing again in the more recent years, which is likely to increase demand for its services.

Recent numbers estimate the size of the CDMO market at around US$ 62 billion in annual revenue. The market is dominated by a handful of large firms due to high barriers to entry. Also, there has been significant consolidation in the CDMO industry recently to improve scale and better serve the needs of the big pharma industry. An example of such consolidation is the acquisition of Juniper Pharma by Catalent in August 2018, or the acquisition of Halo Pharma by Cambrex in July 2018.

Going forward, the expected continued growth of the drugs market due to long-term trends of an aging global population will likely favour CDMOs who can offer scaled production services.
CHALLENGES GOING FORWARD

PRICING ISSUES AND PRESSURES FROM GENERICS AND BIOSIMILARS

Pricing pressures persist and have intensified in the last two years. Payers are increasingly aware of pricing issues and are making concerted efforts to control price increases.

Biologics tend on average to be more expensive than small molecule medicines, and contribute disproportionately to the overall Health Care bill of payers. Biologics are, therefore, in the priority firing line for pricing pressure from governments.

As of 2016, a third of the US prescription drug expenditure (i.e. US$ 105 billion out of US$ 328 billion\(^4\)) was spent on biologic drugs, and they represent two thirds of prescription drugs expenditure for Medicare Part B plan. Globally, even though on a prescription basis, biologics represent around a quarter of all medicines prescribed, the share of the total spend dedicated to biologics is significantly higher.

In the US, political rhetoric around drug pricing was intense during the 2016 election campaign and has picked up again around the mid-term elections in November 2018. How quickly this rhetoric will translate into concrete policies and what shape these policies might take is anyone's guess. So far potential changes talked about have included pegging US market prices to average prices charged internationally. The concept of paying for results has also been widely debated but remains difficult to capture into concrete measures until the backbone infrastructures and data required for this are put in place across the sector.

However, one of the signs that regulators mean business with regards to ensuring that the biopharmaceutical industry remains com-

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**Figure 9:** PwC Health Research Institute analysis of FDA facility registration data, Sep. 2018

Number of FDA-Registered Medical Product Manufacturing Facilities Worldwide

- **Number of device facilities registered**
- **Number of drug facilities registered**
- **Total foreign device facilities registered: 14,712**
- **Total foreign drug facilities registered: 4,130**

- **Canada**
  - Number of device facilities registered: 830
  - Number of drug facilities registered: 233

- **United States**
  - Number of device facilities registered: 25,102
  - Number of drug facilities registered: 6,266

- **Mexico**
  - Number of device facilities registered: 124
  - Number of drug facilities registered: 95

- **United Kingdom**
  - Number of device facilities registered: 764
  - Number of drug facilities registered: 155

- **Norway**
  - Number of device facilities registered: 265
  - Number of drug facilities registered: 42

- **Germany**
  - Number of device facilities registered: 1,222
  - Number of drug facilities registered: 230

- **Switzerland**
  - Number of device facilities registered: 316
  - Number of drug facilities registered: 96

- **China**
  - Number of device facilities registered: 4,124
  - Number of drug facilities registered: 725

- **South Korea**
  - Number of device facilities registered: 1,020
  - Number of drug facilities registered: 491

- **Japan**
  - Number of device facilities registered: 576
  - Number of drug facilities registered: 166

- **Taiwan**
  - Number of device facilities registered: 1,049
  - Number of drug facilities registered: 60

- **Hong Kong**
  - Number of device facilities registered: 482
  - Number of drug facilities registered: 60

- **Malaysia**
  - Number of device facilities registered: 204
  - Number of drug facilities registered: 176

- **Australia**
  - Number of device facilities registered: 211
  - Number of drug facilities registered: 45
petitive has been the introduction in October 2018 of a legislation that bans “gag” rules in the biologics and biosimilars space. 

Similar regulations have existed in the small molecule space since the introduction in 2003 of the Medicare Modernization Act (MMA) which required all patent settlements between originator and generic drug makers to be filed with FTC and DOJ, for their review and potential enforcement against anti-competitiveness. With the October 2018 bill proposed by Senator Brown, the MMA remit will extend to biologics and biosimilars, therefore enabling pharmacists to inform customers of cheaper biosimilars alternatives. This means that the likes of AbbVie’s multiple Humira patent settlements, designed to protect the established reference drug and to delay the US launch of a biosimilar until 2023, will going forward be subject to intense scrutiny by the regulator, just as a small molecule patent settlement would have been since 2003.

This certainly is great news for payers, as in some instances significant savings can be made by payers from getting their patients to switch from reference drugs to biosimilar products. Indeed, it has been estimated by Express Scripts, that switching to biosimilars developed for 11 established biologic products, including Neupogen and Avastin, could save payers around $250bn over a ten-year period. According to Express Scripts, “with an expected cost of 15% to 40% less than originator products, biosimilars create a significant savings opportunity across the U.S. Health Care system.”

However, the extent of immediate savings to payers may not be as obvious as one may have expected. The advent of biosimilars has long been in the pipeline, but has in practice been slow to come through due amongst other things to slow regulatory processes.

The European Medicines Agency (EMA) has been relatively more prolific in its approval of biosimilars, with the first approval dating back to 2006 and a total of 40 biosimilars’ approvals since. The FDA has lagged the timetable significantly, with the first biosimilar drug finally authorised for the US market in 2015. The higher total count of products approved in 2017 and 2018 have included some biosimilars bringing the total number of biosimilars approved for the US market to 15.

Some other headwinds to biosimilars remain. A significant factor is the required education of physicians and patients across the market in the benefits and safety of biosimilars. It has also been argued that the fact that not a single biosimilar has been labelled as “therapeutically interchangeable” has created confusion with physicians and patients and has slowed down adoption.

However, the political will and the current US administration’s combative rhetoric focused on lowering drug prices will in any case give support to both generics and biosimilars companies, and competition from both will increasingly be a factor to contend with for originator biopharmaceutical firms.

The slowdown in Obamacare enrolments and the effect of pricing pressures from payers, together with re-introduction of trade tariffs present short- to medium-term challenges which will require continued adaptability by the sector

RETURN OF TRADE TARIFFS

Further, the introduction of tariffs by the US to apply to their trade with countries such as China, Canada and Mexico is expected to come into force in 2019. These tariffs and the retaliatory tariffs imposed by China are expected to affect pharmaceutical and medical device sectors the most, as these have the most international supply chains. PwC estimate that worldwide there are “more than 18,800 medical product manufacturing facilities that are registered with the FDA representing more than US$ 167 billion in annual value.” Depending on their provenance they will be more or less affected by new tariffs.

However, a number of supporting factors are likely to facilitate the growth of the Health Care sector going forward.

49. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm
SUPPORTING FACTORS

GLOBAL POPULATION IS AGING AND CHRONIC CONDITIONS ARE ON THE RISE

The percentage of population over 65 years old keeps increasing in all major economies. The incidence of chronic disease is also on the rise, not only in the developed economies, but equally across the Asian continent, notably in China and India with the increase of diabetes. Demand for drugs focused on managing long-term conditions is expected to continue increasing.

UNIVERSAL HEALTH CARE PROGRAMS AND GROWTH MARKETS

Also, universal Health Care provisions are being slowly but surely rolled out across a number of developing economies, including some major economies in Asia. India is one such example, where the National Health Protection Scheme is to be rolled out from 2019 to cover 500 million people with lower incomes52.

Other economies across Asia Pacific are also expected to grow their demand for Health Care products and services. Among these is Indonesia, where the compound annual growth rate of Health Care expenditure is expected to be as high as 9.6% between 2018 and 2021, ahead of the expected GDP growth rate at 8.4% an-


Percent of Population Over 65 years Old

Figure 10: United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects, The 2017 Revision.
The world's population continues to age and chronic disease is on the rise, both in developed and emerging economies. Additionally, continued adoption of universal health care coverage systems, together with the emergence of consumer-centric connected care will serve as sources of long-term growth for the global Health Care sector.
nually over the same period, supported by the roll out of universal health coverage\(^5\). According to the EY report\(^5\), the high growth markets of Asia Pacific, today collectively representing an annual Health Care expenditure of US$ 123.8 billion, are likely to provide a further uplift in demand for medicines and medical services going forward.

**CHINA’S EMERGENCE AS A R&D AND ACQUISITIVE POWER**

China is already the world’s second largest pharmaceutical market behind the US and is expected to grow further with the rise in incidence of chronic diseases. It is expected that China’s population of over 65s will grow to around 350 million people by 2050. China’s demand for health-related products and services is expected to explode in the coming decades. As of 2016, 64% of pharmaceutical sales in China are generics, with only around 22% being spent on patented drugs.

China is committed to developing its own generics manufacturing capabilities, having experience essential drugs shortages in the recent past. It is also investing in its own R&D capabilities. China’s investment in pharmaceutical R&D has grown from US$ 163 million back in 2000 to US$ 7.2 billion as of 2016\(^5\). Further, the last few years have seen the emergence of the Chinese biotechnology industry with its output expected to reach 4% of the country’s GDP by 2020\(^5\).

Finally, China has more recently also become a source of investment into the Health Care sector globally. For example, the insurance and financial company Ping An launched its Global Voyager Fund to invest US$ 1 billion in worldwide FinTech and Health Care start-ups\(^5\). Chinese funds have been active in the global Health Care buyout space, as illustrated by the Bain report below\(^5\), with over half of 2017 Chinese deal value directed at overseas targets.

**INDIA RAMPING UP R&D EFFORTS**

India, the world’s largest provider of generics with 20% global market share, is also no longer content with its focus on generics only and has been ramping up its investment in biopharmaceutical R&D. This recently stands at around US$ 1.9 billion in 2017\(^5\), up from US$ 480 million back in 2008. Further, having been dependent on China for imports of up to 66% of its APIs, India has been taking steps to offer subsidies to local drug makers to encourage local API manufacturing\(^5\).
EMERGENCE OF INTEGRATED, CONSUMER-CENTRIC AND PREVENTION-FOCUSED HEALTH CARE

The increasing focus on integration of care with use of digital wearables and the continuous emphasis on collecting large amounts of data through digital diagnostics will in time lead to an integration of Health Care provision as a service, as well as a shift to Health Care becoming increasingly consumer-centric putting the individual patient in control of their health. Further, a shift in focus from condition treatment to prevention and identifying potential conditions early is expected to be supported by advances in genetics-based research.

Technology and retail giants such as Amazon are increasingly interested in the health care space where they see a number of inefficiencies. They want to leverage their existing platforms to extend their business models into health care service provision, with a vision to provide a closed loop array of services including virtual health facilitation, diagnostics and preventative care. Amazon’s partnership with Berkshire Hathaway and J.P. Morgan to provide employer health services, as well as its entry into pharmacy space with the acquisition of internet pharmacy PillPack, and the introduction of more health products on its existing platform are all initiatives designed to lead its foray into the health care services.

SO WHERE DOES ALL THIS LEAVE ALLOCATORS?

The Health Care sector is extremely diverse, as it includes product-focused firms such as biopharmaceutical and medtech firms collectively representing approximately 75% of the sector’s market capitalization, as well as service providers, such as hospitals. It is heavily regulated, and often requires specialist knowledge to understand the underlying scientific basis for products, which can make it a maze to navigate. Expertise in legal and regulatory frameworks is often required to understand the dynamics of the sector in various jurisdictions and to be able to accurately value biopharmaceutical companies’ pipelines based on their chances of success at various R&D and approval stages. Also understanding and correctly assessing the latest political influences that may sway the sector into one direction or another also requires in depth insight into political currents that will likely have impact on Health Care regulators.

For investors interested in going over and beyond simply passive exposure to the sector, and desiring a more nuanced approach to benefiting from long-term trends in Health Care, it is essential to pick a handful of specialist managers to allocate to, who will command expertise in their specific niche and enable investors to focus on the right opportunities at the right time.
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