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Pharma R&D Annual Review 2019

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Introduction

Welcome to Pharmaprojects' 2019 review of trends in pharmaceutical R&D. For over a quarter of a century now, I've been taking an annual look at the evolution of pharma R&D, and in this article, I'll look at the state of play at the start of 2019. We'll assess the industry trends by examining the pipeline by company, therapeutic area, disease, target and drug type, using data from Informa Pharma Intelligence's Phamaprojects, part of the Citeline suite of products, which has been tracking global drug development since 1980. This report will be followed up by our annual supplement reviewing the New Active Substance launches for the year just passed. But here, we will be focusing on research and development as it is now, and identifying its winners and losers, looking at a number of league tables, and seeing who is emerging as champion, and who is staring relegation in the face.

After taking a musical motif in the 2018 report, this year I've chosen a theme which very much reflects the underlying competitive nature of pharmaceutical R&D – sport. Although most sports started out as fun pastimes to be enjoyed outside of the working week, their professional versions are now often multimillion-dollar businesses, where, like pharma, tiny decisions can have huge consequences. Drug development is clearly no game either – for many patients, it is literally a matter of life and death. Some sportsmen and women would contend that for them, figuratively at least, the same applies to their chosen endeavour. I'm reminded of a famous quote by Bill Shankly, the legendary former coach of UK football team Liverpool FC who spent 15 years in charge: "Some people think football is a matter of life and death. I don't like that attitude. I can assure them it is much more serious than that." And in another sense, for the pharma companies themselves, corporate survival depends on the repeated successful delivery of new drugs to the market.

How else is sport like pharma? Let's draw some further analogies. As every Englishman knows, the greatest sport in the world is cricket. In its purest form, the test match, a single game can last five full days, the sporting world's equivalent of the marathon length of drug development times. There are many other similarities between a test match and pharma R&D. To those on the outside, its rules and rituals can often appear abstruse. Fortunes may ebb and flow over the course of the game. Everything may appear to be progressing serenely, only for some bad clinical results to change the course of proceedings like the clatter of a bunch of quick wickets. And just as, somewhat mystifyingly to those not familiar with the sport, there may be no winner even after five days' play is completed, there's not always a clear result at stumps on day five in R&D. Drugs make it on to the market, only to fail to grab market share and to end up losing money. Similarly, a potential big hitter might be 'out' early, but this might give an unfancied tail-ender their chance to shine and to score a maiden century. There's certainly seldom a safe bet in either arena.

Or how about team field sports such as football (both soccer and American) or the various forms of rugby and hockey? These feature multiple routes towards the goal, try or touchdown, many of which are thwarted, and thus require a reassessment of strategy, just like clinical development. There are barriers to overcome at all points. And maybe only 1% of attacking moves will ultimately result in a score, just as only 1% of drugs entering the clinic eventually find a path through to the market.

My own sport is badminton, and as I've probably passed the middle point of middle-age, I restrict myself to doubles matches these days, singles being far too aerobic. The doubles game is highly dependent on good positional play, as one's opponents are always on the lookout for gaps to send the shuttlecock into, in the same way that pharma must seek to exploit gaps in the market. Unlike drug development though, badminton is fast. A game usually only takes 10 minutes. And it's a little-known fact that the shuttle can travel faster than the projectile in any other sport – regularly moving at more than 100 miles per hour. In fact, while testing out new racket technology in 2013, Malaysia's Tan Boon Hoeng set a new world record with a 493km/hr (306mph) smash! Thus, quick reflexes and agility are the attributes of my sport, which I would say the pharmaceutical industry needs most.

So, let's fire the starting pistol/blow the whistle/wave the starting flag on this year's R&D Review event. There will be winners and losers, medals to award, high-flying newcomers, and players forced to retire. If there's one thing a sports fan loves, it's statistics. And so do we here at Pharmaprojects!

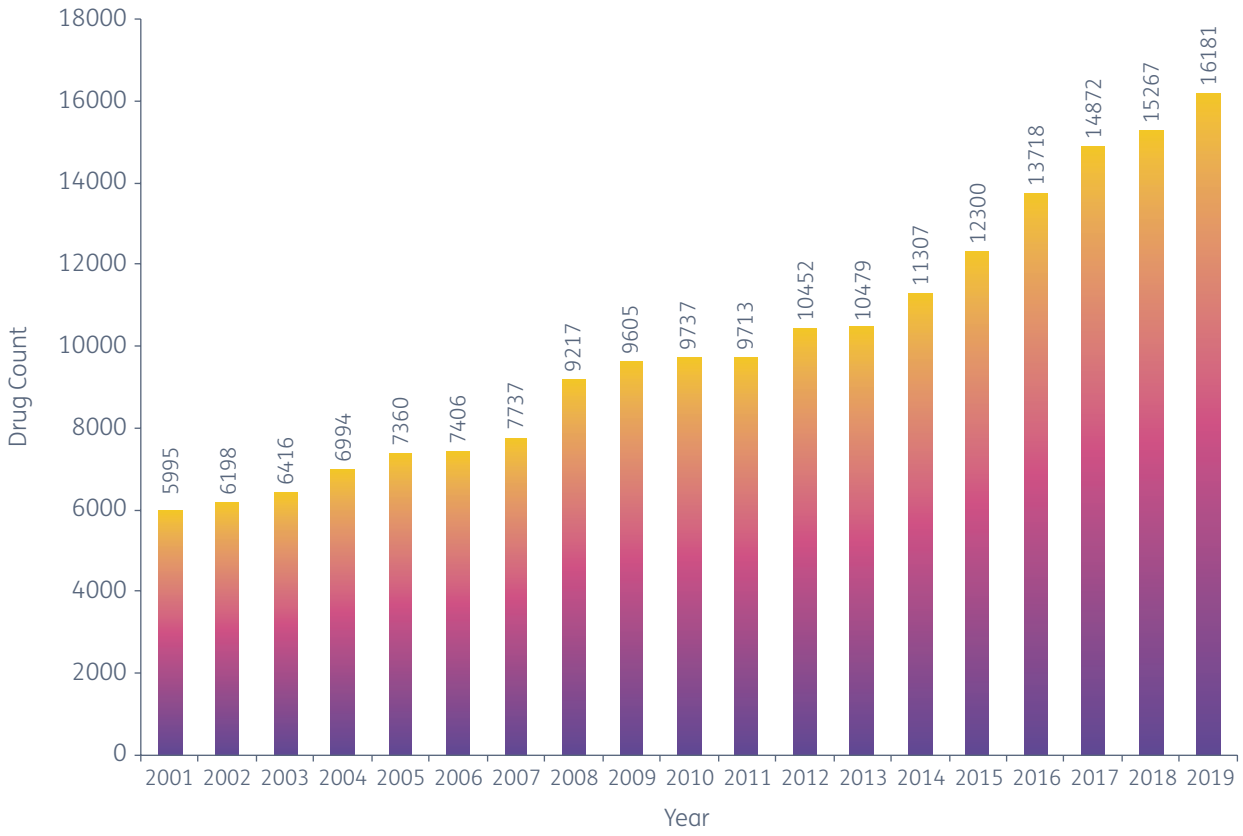
Total Pipeline Size

World record again for 2019

We begin our Olympic-sized statistical tournament with the highlight from our own Opening Ceremony – the reveal of the headline figure of the total number of drugs in the R&D pipeline. By pipeline here, we mean that we are counting all drugs in development by pharmaceutical companies, from those at the preclinical stage, through the various stages of clinical testing and regulatory approval, and up to and including launch. Launched drugs are still counted, but only if they are still in development for additional indications or markets. Will the torch be burning brighter than last year once again?

The answer is yes, as Figure 1 shows. Just as in sports, where the limits of human endeavour are forever being extended by new world records, the pipeline continues to reach new heights each year. For 2019, the growth rate is just shy of 6%, making this a more robust expansion than the 2.7% delivered for the previous year. The new top score is 16,181 drugs in R&D. Looking over the past three years, we've seen rises of 8.41%, 2.66% and 5.99%, which averages out at 5.69%, making the 2019 growth rate slightly above the three-year mean. This is a highly respectable performance during a year of ongoing political instability.

Figure 1: Total R&D pipeline size, by year, 2001–19



Source: Pharmaprojects®, January 2019

However, just because there are more runners and riders this year, it doesn't necessarily mean that more competitors have successfully jumped over all the hurdles, completed the course and crossed the finishing line. To extend the horseracing analogy further, a more crowded field can often lead to more casualties. The UK's premier steeplechase race, The Grand National, has been notorious over the years for having multiple fallers over its treacherous 30-jump course. The apotheosis of this was the 1928 race, when *Tipperary Tim*, a 100/1 outsider, took the tape as one of only two finishers from a 42-horse field. So how many new drugs successfully romped home during 2018? While we are still in the process of curating our data on new active substance (NAS) drug launches for the year, and will report this and highlight other NAS trends and innovative drugs in our NAS Supplement to this report, preliminary figures indicate that over 60 new drugs hit a home run during the last calendar year. The US FDA had a record year, approving 64 new molecular entities and novel biologics in 2018. This may prove tough to beat in 2019, especially as, at the time of writing, the FDA remains closed for business due to the record-length US government shutdown.

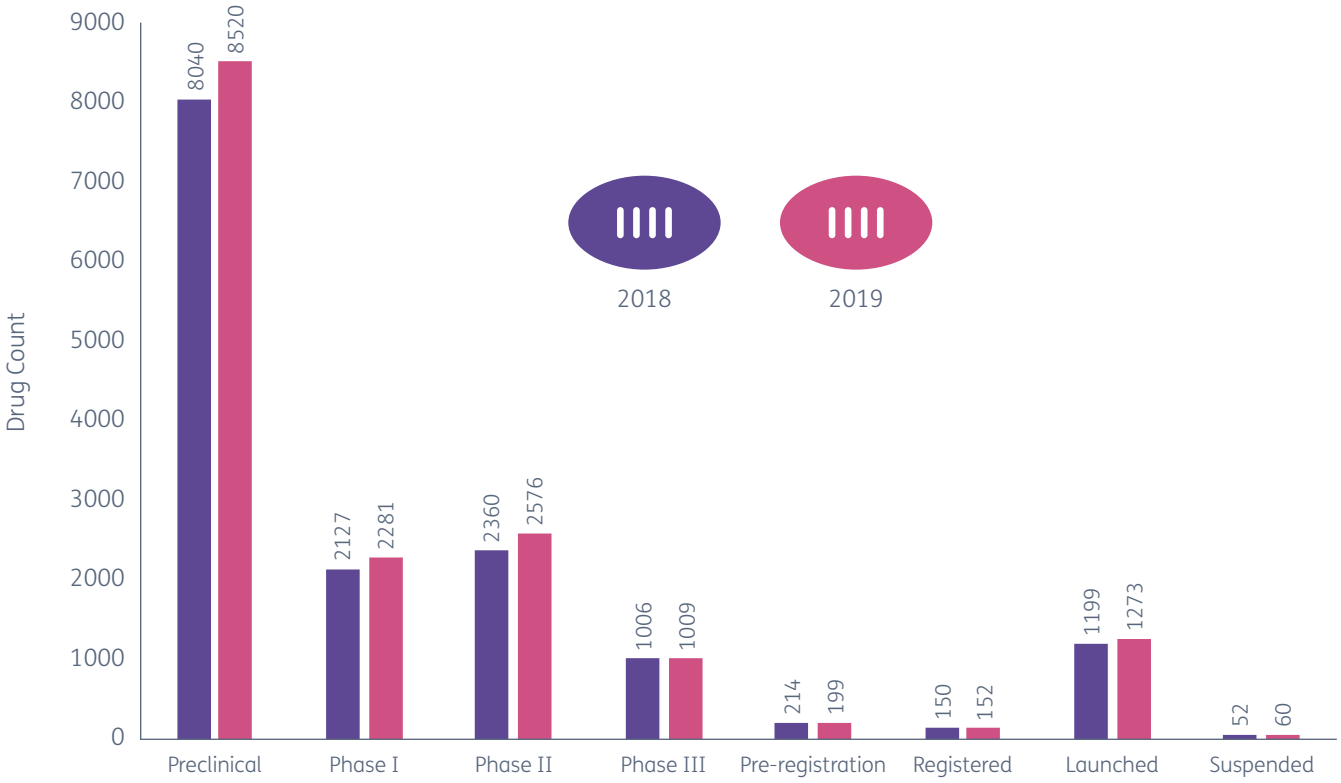
The 2019 Pipeline by Phase

Fallers at Phase II still holding up the field

If we break the pipeline down to the various stages of the race to the finish line, a somewhat less encouraging picture emerges. Long-distance runners and endurance cyclists often talk about 'hitting the wall' or 'the bonk': a point latish in the race where they are hit by the obstacle of a sudden and catastrophic loss of energy. Some push through to complete the course, but for many, this spells the end of the road, and they are forced to retire. Breaking down the R&D pipeline by phase (see Figure 2) would seem to indicate that pharma continues to hit its own version of the wall – Phase II trials.

Things are looking good as the starting pistol is fired, with a 6% increase in the number of drugs at the preclinical phases, very much in line with the overall rate of pipeline expansion, although down a bit on last year's 7.3% increase. This is despite an actual uptick in the number of drugs newly added to the Pharmaprojects database over the past 12 months, which hit 4,001 debutants last year. This is up significantly from the 3,807 added during 2017, and is just four shy of 2016's record-breaking number.

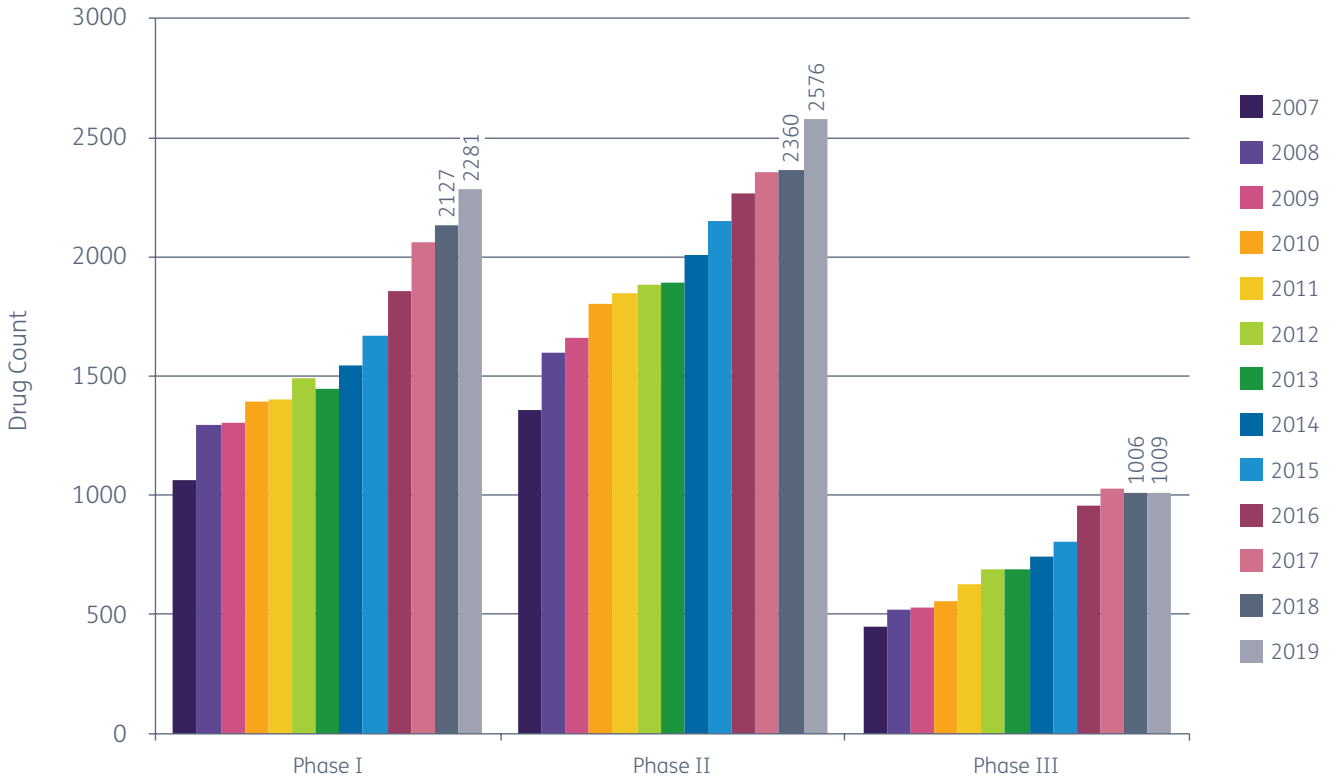
Figure 2: Pipeline by development phase, 2019 versus 2018



Source: Pharmaprojects®, January 2019

The number of drugs in Phase I has increased by a more impressive 7.2%, much more than the 3.0% seen last year. The state of play at Phase II is even better: following a flat 2018, the increase here is a whopping 9.2%. But from there, matters have gone somewhat awry, as a good portion of the pharma field appears to leave the fairway and head straight for the bunker. The number of drugs in Phase III hasn't gone up at all, while figures for those on the home stretch and heading for the clubhouse – those awaiting approval or launch – have actually posted a 3.6% decline, even worse than 2018's 1.9% drop. So, it would seem that failure at Phase II still behaves like that long-standing niggling knee injury that just won't go away, however much the physio works on it. This trend is again emphasized if we look further back through the years at the numbers of drugs in each clinical stage (Figure 3). This suggests that, rather than breaking through the Phase II pain barrier, the situation is steadily worsening, with a greater percentage of drugs reaching Phase II having to leave the field.

Figure 3: Clinical phase trends, 2007–19



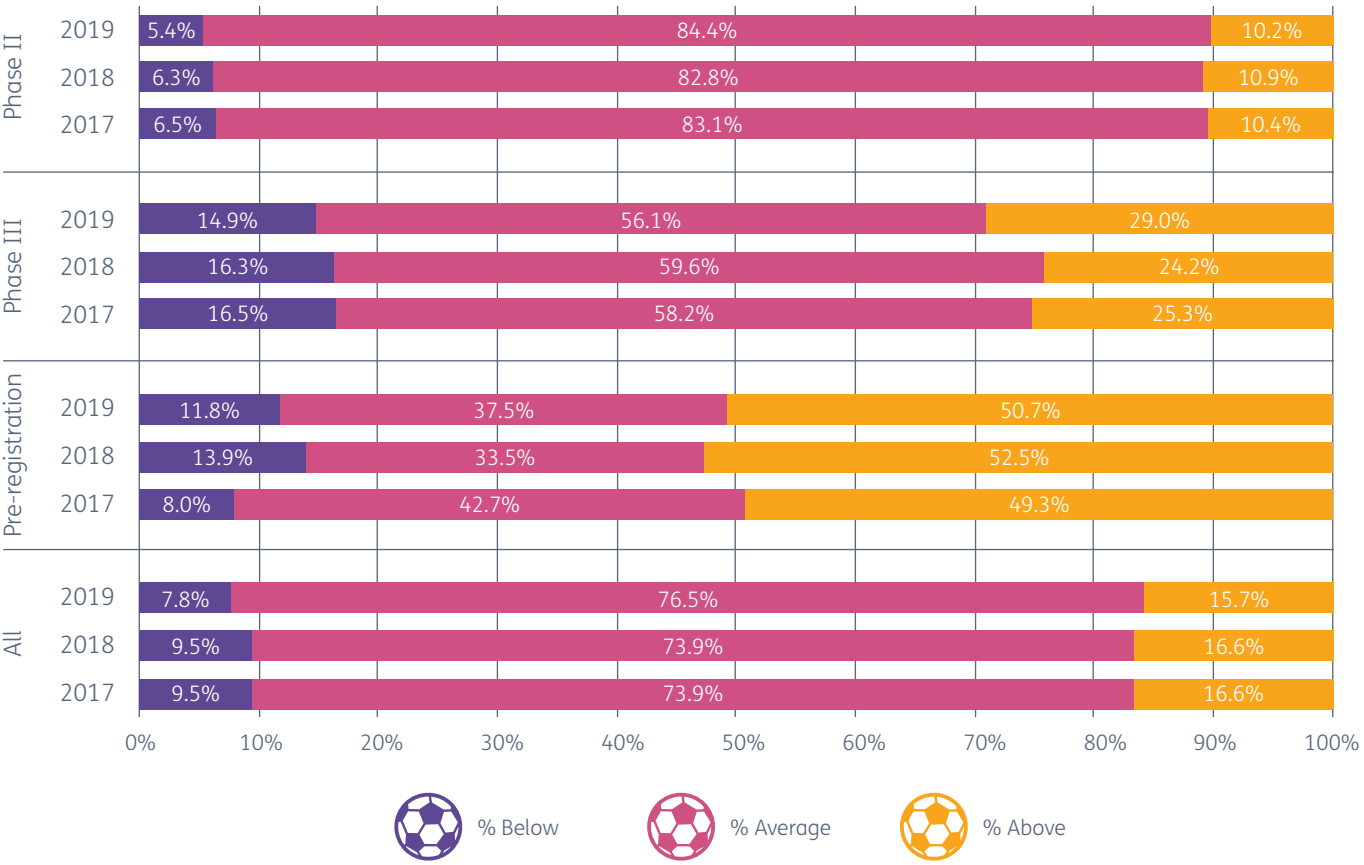
Source: Pharmaprojects®, January 2019

Although the number of launched drugs featured in Figure 2 rose by 74 (6.2%) to 1,273, this doesn't quite tell the full story, since these are only the 'active' launched drugs: those which are on the market but still under active development for sales in additional countries or additional indications. In all, 108 drugs underwent their first launch during 2018 – similar to the number in 2017 – but this rise was slightly dampened down by drugs moving to the 'fully launched' category, as they are no longer being rolled out further and their development is essentially complete.

However, having more drugs in R&D (which is enormously expensive) without launching any new drugs is akin to having an inflated wage bill for your team without winning any medals or cups. In both cases, that's not sustainable. So, all eyes will be on our NAS Supplement report to see which teams will be touring the city on a victory lap in an open-top bus, and which will be telling their players to get on their bikes.

One guide to how our pharma team might fare in upcoming seasons is to look at drugs' likelihood of approval, based on milestones and reported results as they pass down the pipeline. This is what analysts at one of our sister publications, Biomedtracker, do. They examine clinical and regulatory events in order to place their own weighting on a drug's likelihood of approval (LOA) by the FDA, and determine whether a drug is more likely, as likely, or less likely to be successfully approved than other drugs for the same disease. Figure 4 visualizes this data for 2019 by phase, from Phase II to pre-registration, and compares it to the equivalent data for the two previous years. There is also rolled-up data for the entire Phase II to pre-reg population.

Figure 4: Distribution of likelihood of approval ratings for pipeline drugs in Phase II to pre-registration, 2017–19



Source: Biomedtracker, January 2019

Back at Phase II, for most drugs, there aren't enough data readouts to move the LOA much from the mean. By Phase III, this is changing, and there is also encouraging news here. This year, 29.0% of drugs in Phase III are assessed as having a greater than average likelihood of approval, up from 24.2% last year. However, this trend is reversed by the time we get to pre-registration. So it's a bit tricky to draw too many conclusions about the quality of the pipeline, and in any case, as any betting man who likes a flutter on the gee-gees will attest, past form is rarely a good guide to future performance!

Top Companies

Takeda's acquisition of Shire propels it into the premier league

Let's move to look at pharma's big hitters – the Top 25 pharma companies by pipeline size for 2019. Who's knocked the ball out of the park? Who looks most like hitting a home run? And who has been struggling to reach first base?

Winning the World Series for a third consecutive year narrowly is Novartis. As Table 1 shows, it not only has the largest pipeline, but it has by far the most originated drugs, with 60% of its portfolio being developed in-house. This is the highest percentage of any of the companies in this year's Top 10. Having said that, in terms of new drug launches, the Swiss multinational heavyweight could be said to have had a less than stellar year, with no Novartis-originated molecules among its three new launches. Its major new release was Aimovig (erenumab), which it in-licensed from Amgen, and was one of three calcitonin gene-related peptide (CGRP) receptor antagonists launched during 2018 for the prevention of migraine (the others were Pfizer's Ajovy [fremanezumab] and Eli Lilly's Emgality [galcanezumab]). Aside from this, it also licensed-in Spark Therapeutics' innovative but very niche gene therapy for blindness caused by RPE65 gene mutations, and its generics division Sandoz launched a biosimilar version of AstraZeneca's anti-TNF antibody, adalimumab. So, Novartis may sit at the top of the league, but it has spent a lot of money bringing new players into the side with comparatively little prize money in return last season. This year, it will need to keep its eye on the ball.

When sports teams feel that they are struggling or need to shore up their strength, there are two options open to them. The licensing-in option in pharma is akin to a club buying in some new players to bolster a perceived weakness in, say, defence, or in goal scoring. This summer, LeBron James, one of the greatest basketball players of this generation and a global sports icon, left the Cleveland Cavaliers, having been poached by the Los Angeles Lakers. He is one of the most impactful players on the court because he can singlehandedly carry his teams to victory. The Lakers knew what they needed and were prepared to pay to get it – he is reportedly on a four-year, $153.3m contract.

The other option is wholesale acquisition or merger. This is less common in the sporting world, but there have been some well-known examples over the years, especially in soccer. The English league is littered with clubs with 'United' as part of their names, such as Newcastle United, which can trace its roots back to the merger of Newcastle West End and Newcastle East End in 1892. More recently, in Japan, Kagoshima United FC was created by the 2014 merger of Volca Kagoshima and Osumi NIFS United. And there are multiple examples of takeovers of clubs by individuals or organizations outside of the sport, such as Russian oil oligarch Roman Abramovich's ownership of Chelsea, and Fenway Sports Group's acquisition of Liverpool FC to go with its US baseball team, Boston Red Sox.

This year, we see a new runner-up in our league, thanks to one of the biggest acquisitions in years – that of Shire by Takeda. This completed just as our 2019 data were being compiled, and thus we are yet to see the results of any post-merger pipeline consolidation, and could reasonably expect to see the combined entity somewhat shrink its pipeline in the coming months. As things stand though, it catapults Takeda up to number two in the table, the highest position ever reached by a Japanese-headquartered company.

A further big merger affecting the Top 10 was revealed in the first days of 2019, with Bristol-Myers Squibb announcing that it will acquire Celgene. That particular transaction won't complete until the third quarter of this year, but if we take a simple additive approach, including the 98 drugs in Celgene's pipeline would return BMS to the Top 10, pushing it up to joint third in the league. According to Informa's Pharma Insight publication, Scrip, *"The transaction represents the fourth-largest biopharma acquisition to date, only slightly behind Takeda/Shire ($79bn) from earlier last year and trailing Glaxo/SmithKline ($78bn) in 2000 and Pfizer/Warner-Lambert ($84bn) in 1999. Amidst investor scepticism regarding future growth and the risk Bristol-Myers is assuming with the deal's high price tag, the parties hope the combination will provide immediate growth potential and leverage the strengths of*

both, particularly in oncology and combination therapies. The merged entity takes on Celgene's complementary assets in the oncology, immunology, and inflammation spaces, along with Bristol-Myers' cardiovascular programs."[1] Adjusted for inflation, this is reportedly going to be the largest pharma M&A deal since the heady days of 1999. Celgene has meanwhile posted a significant climb up the table itself, rising from 20 last year to 14 this.

It's been a while since we saw two big M&A deals affecting the Top 10 teams (there were none at all through 2017). Does this change indicate the ushering in of a new era of mega-merger activity? Most analysts think not. EY Global Life Sciences' transactions leader, Peter Behner, quoted in the Scrip article cited above, pointed out that: *"The same factors that held down biopharma M&A in 2018 still apply. Potential buyers remain in hold mode due to what they perceive as high valuations for the available companies and assets as well as concerns about geopolitical uncertainties, such as the pricing environment in the US"*.[1] There have been smaller, niche acquisitions among the premier league teams, including Novartis's purchase of Endocyte, AveXis and Advanced Accelerator; Takeda's acquisition of TiGeniX; Johnson & Johnson buying ImmuneTarget and BeneVir; Sanofi acquiring Ablynx and Bioverativ; Roche's takeover of Tusk Therapeutics, Merck & Co's acquisition of Viralytics; and Eli Lilly's purchase of AurKa Pharma and ARMO Biosciences. It's likely that this strategy of acquiring players with key skills will continue in 2019, with Eli Lilly already announcing its intention to add Loxo Oncology to its squad.

Table 1: Top 25 pharma companies by size of pipeline

Position 2019 (2018)	Company	No of Drugs in Pipeline 2019 (2018)	No of Originated Drugs 2019
1 (1)	Novartis	219 (223)	131
2 (9)	Takeda	211 (164)	99
3 (2)	Johnson & Johnson	208 (216)	112
4 (3)	AstraZeneca	194 (205)	111
5 (4)	Sanofi	192 (179)	93
6 (5)	Roche	189 (191)	106
7 (7)	GlaxoSmithKline	177 (191)	99
8 (6)	Merck & Co	176 (191)	86
9 (4)	Pfizer	163 (192)	96
10 (11)	Eli Lilly	124 (121)	74
11 (10)	Bristol-Myers Squibb	110 (134)	73
12 (12)	Bayer	108 (111)	77
13 (18)	Otsuka Holdings	98 (89)	59
14 (20)	Celgene	98 (85)	40
15 (15)	AbbVie	94 (98)	31
16 (16)	Boehringer Ingelheim	94 (92)	59
17 (14)	Daiichi Sankyo	92 (105)	49
18 (13)	Allergan	90 (108)	37

1. Scrip (2019) Bristol/Celgene Made Perfect Sense, But Doesn't Promise Big M&A Year, EY Says. Available from: https://scrip.pharmaintelligence.informa.com/SC124460/BristolCelgene-Made-Perfect-Sense-But-Doesnt-Promise-Big-MA-Year-EY-Says [Accessed 17 January 2019].

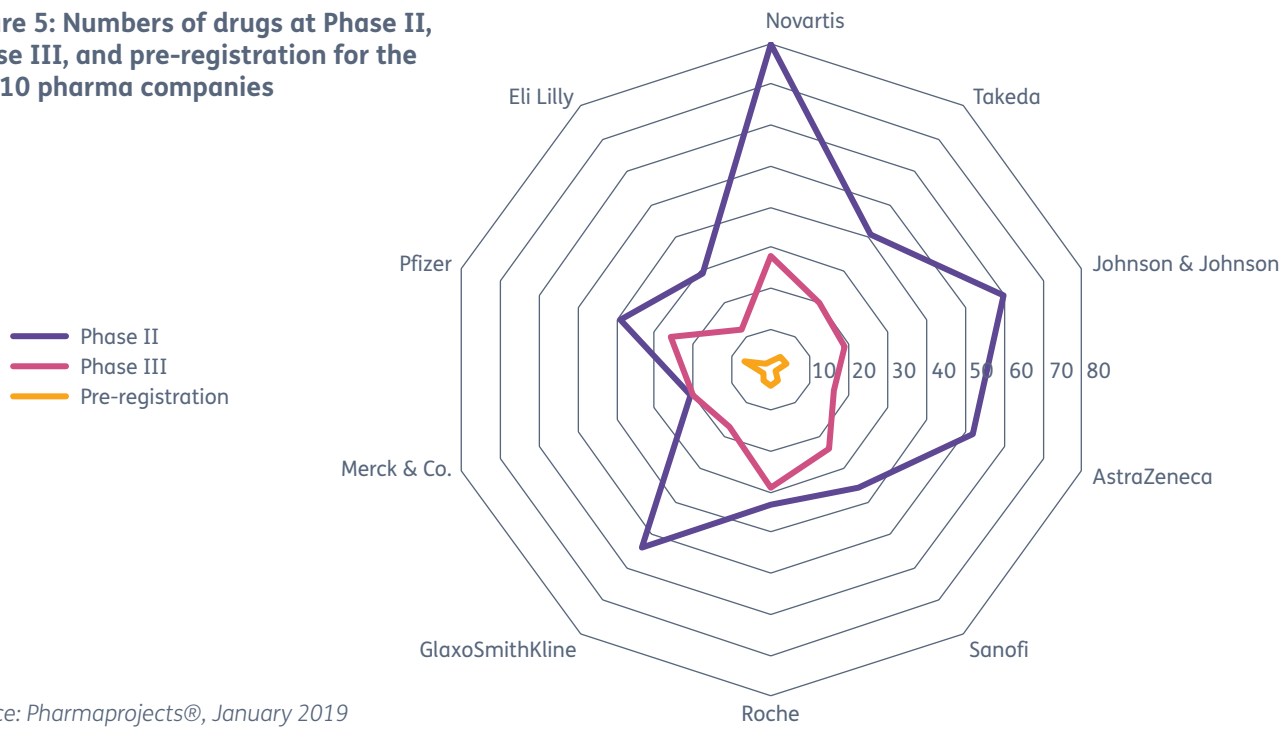
19 (19)	Amgen	88 (87)	58
20 (21)	Eisai	85 (84)	49
21 (17)	Astellas Pharma	84 (92)	44
22 (25)	Ligand Pharmaceuticals	73 (65)	28
23 (23)	Gilead Sciences	69 (66)	47
24 (-)	Evotec	63 (-)	34
25 (-)	Biogen	62 (-)	14

Source: Pharmaprojects®, January 2019

Elsewhere in terms of positioning within the Top 10, it is pretty much business as usual, with most of the major league teams shuffling down a place to accommodate the newly merged Takeda-Shire United entity. The exception to this is Pfizer, which continues to ping-pong up and down the table (in recent years it has gone from 2 to 5 to 4 to 7 to 6 to 3 to 4 and now back down to 9). Interestingly, leaving aside the Takeda/Shire partnership, and in a repeat of last year, only two of the Top 10 actually expanded their portfolios in 2019: Sanofi at number 5 and Eli Lilly at number 10. Given the amount of acquisitions team Top 10 Pharma made, as reported above, this indicates an overall organic shrinkage in their drug discovery.

Just how different the complexion of the biggest pharma companies' late-stage pipelines is can be seen in the radar chart in Figure 5. Here, the purple line indicates how many drugs each of the Top 10 pharma companies has at Phase II, the pink line at Phase III. So, while Novartis is currently reporting many more Phase II drugs than Phase III drugs, other companies, such as Merck & Co., have similar numbers at both Phases. As we zoom in towards the bullseye of the centre of the chart and the orange data for pre-registration, we can see how the numbers for all companies shrink considerably.

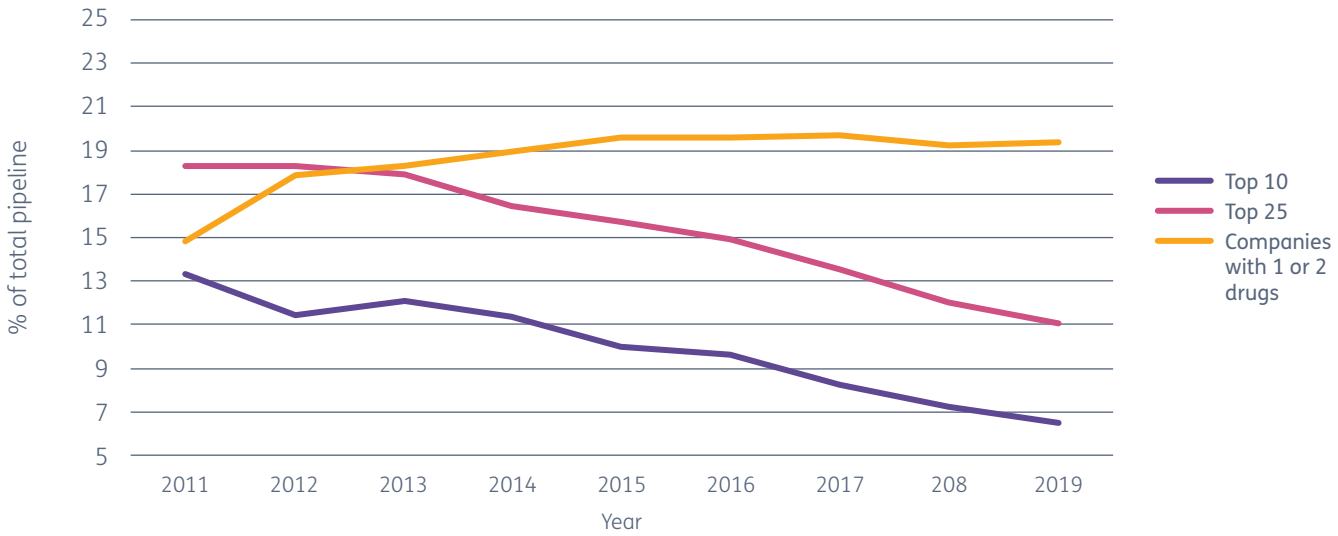
Figure 5: Numbers of drugs at Phase II, Phase III, and pre-registration for the Top 10 pharma companies



Source: Pharmaprojects®, January 2019

The issues which the biggest pharma companies seem to be continuing to face are further highlighted when we examine how the share of the total pipeline which top companies contribute has been shifting over the past few years. In Figure 6, the purple line represents the percentage of drugs in the entire pipeline which originated at the Top 10 pharma companies, and how this has changed over time. From a position as recently as 2011, when this figure was at over 13%, we have seen it steadily decline to the point now where it has more than halved – the Top 10 now only produces 6.45% of drugs. There have been similar falls when this is extended out to the Top 25, which were the source of 18.3% of molecules in 2011, declining to 11.0% today.

Figure 6: Share of the pipeline contributed by Top 10 companies, Top 25 companies, and companies with just one or two drugs

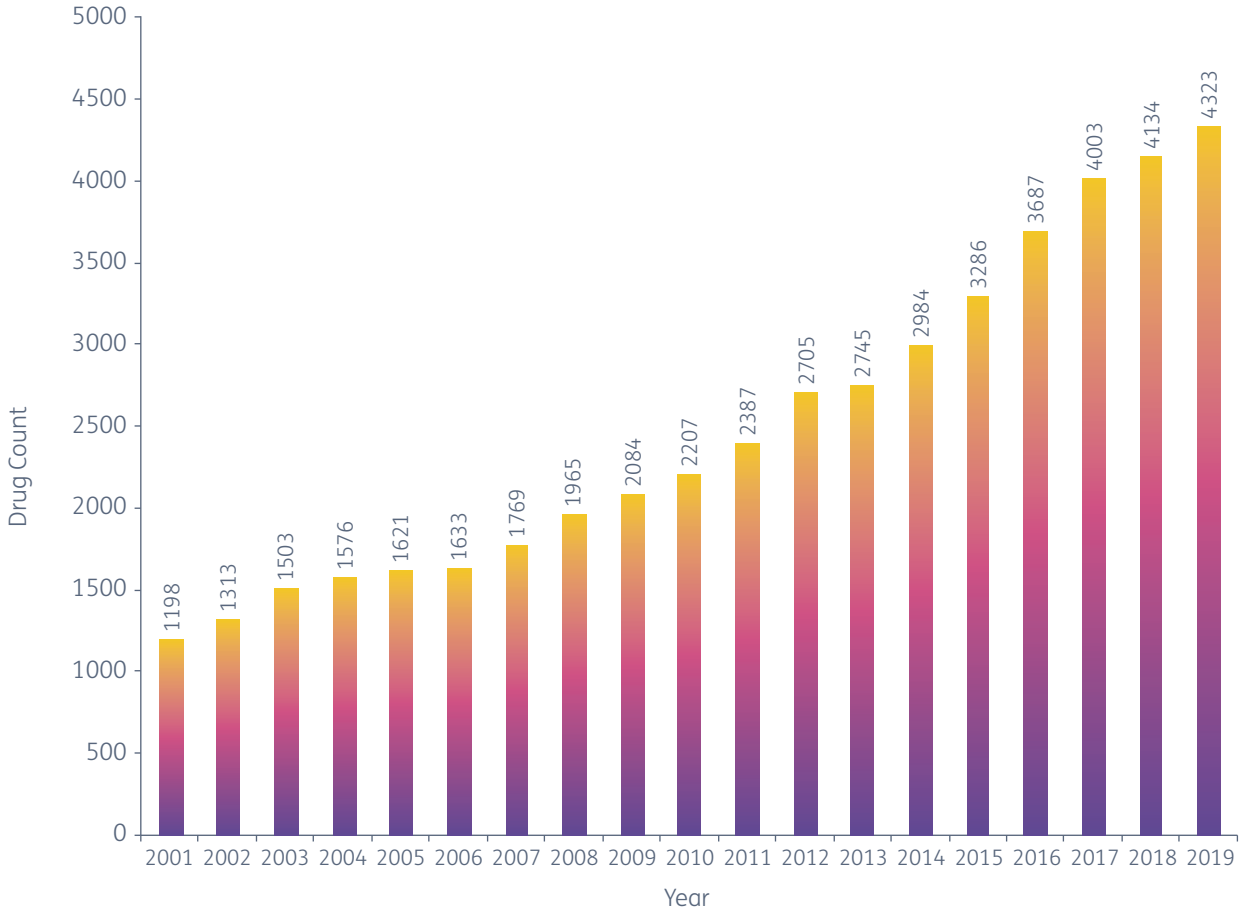


Source: Pharmaprojects®, January 2019

Meanwhile, Figure 6 also shows how the myriad and ever-expanding number of small companies with just one or two drugs have been providing a larger slice of the pie, up from below 15% eight years ago to approaching 20% now, although this hasn't increased much since 2015. The actual numbers of such companies – the equivalent to the local youth team playing in the park on Saturday mornings – didn't change much either since last year. There are now 1,633 companies with just one drug (up slightly from 1,627 in 2018), and 669 with two (up from 657). But, as in sport, this represents a big part of the overall level of participation. These minnows account for 18.3% of the drugs in active development, and a huge 53.3% of the companies involved, although this latter metric posts a decline from 2018's 55.2%.

In terms of the total number of companies participating in pharma R&D this year, like the total number of drugs, the 2019 increase has exceeded that seen in the previous year. As Figure 7 reports, this number now stands at 4,323, up 189, or 4.6%, on the previous total, where the rise had been of just 3.3% in 2018. The increase can largely be attributed to another strong year for the number of new companies entering the race, with 722 new pharma and biotech firms joining in, more than the 670 added during 2017, and close to 2016's record-breaking 750. If 722 firms entered the fray but the total number of companies only rose by 189, this means that through 2018, we lost 533 companies to merger, acquisition, failure, or hibernation – another bigger figure than that seen in the previous year, which was 487. This all adds up to a season with a particularly busy transfer window.

Figure 7: Total number of companies with active pipelines, 2001–19



Source: Pharmaprojects®, January 2019

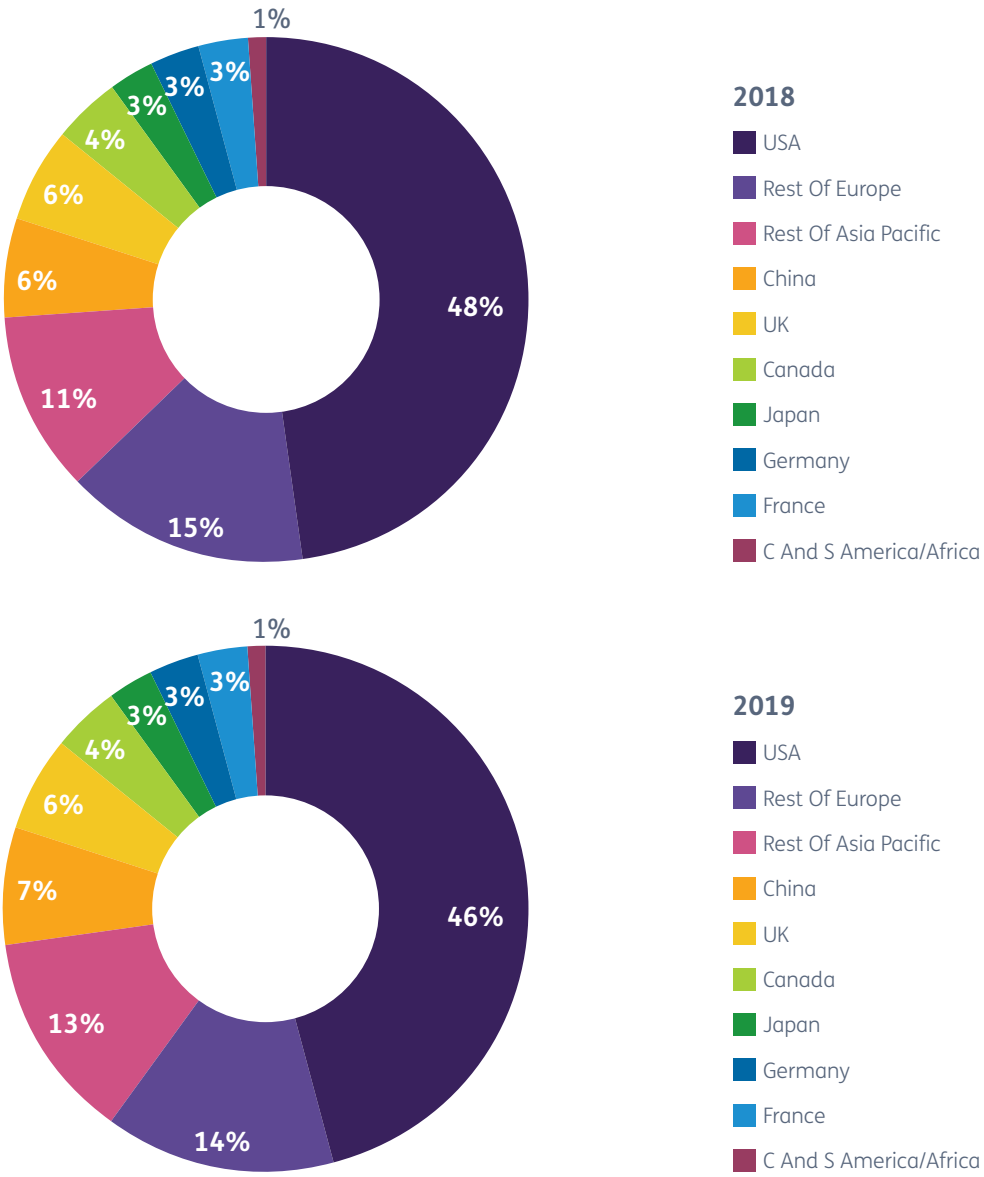
2018 saw the football World Cup finals hosted in Russia – the biggest global single-sport event the planet has to offer. Eventually won by France, the competition was watched by an estimated 3.4 billion people – just below half of the entire global population – with 1.12 billion watching Croatia succumb to *les bleus* in the final match alone. In the UK, where the unfancied England team had a golden cup run matched only by the best summer weather for a generation, it's estimated that 26.5 million people, or 40% of the population, watched it all come crashing down in the semi-final. The soccer competition is reckoned to be the most-watched sporting event ever, its global reach even exceeding that of the summer Olympics. Both easily outstrip the next four big hitters: the European football championships, the cricket World Cup and the Indian IPL league, and the US Super Bowl final. Sporting events have become global events for humanity, transcending regional and racial barriers.

Likewise, the pharmaceutical industry is one of the truly international endeavours of the human race. Go to different parts of the planet and you might see different cars, different beers, different breakfast cereals, but all of the pharmacies will be stocking Prozac. Only telecommunications come close in their global reach – and pharma got there first. However, historically, since the conventional pharma industry emerged from Western societies, it has been very much concentrated in North America and Europe. This has begun to shift in recent years, a trend which Figure 8 shows is picking up pace.

The pie charts here show where pharma R&D is concentrated in terms of where its companies are

headquartered or originate. It shows that in pharma, as in many Olympic sports such as swimming, while the US still dominates, it is beginning to retreat as Asia advances. The graphic shows that while the US still hosts 46% of pharma companies, this has fallen 2%, and is at its lowest recorded level yet. The next single biggest producer of pharma R&D is, for the first time, no longer Canada or one of the major European countries such as France, Germany, Italy or the UK, but rather China. With 301, or 7%, of drug developing companies being Chinese, this continues to be a long-term trend whereby year-by-year, the number of indigenous companies there embarking on development of novel therapeutics, rather than joining its established generics industry, has risen (it's up another 15% this year). Brexit-beleaguered Britain slips to third place as its constituency narrows further. Overall, European-centred pharma companies now account for 25% of the total, down from 27% last year. Meanwhile, the direction of travel is the opposite across Asia, with its share increasing from 20.5% to 23.6%. The amount of territory gained in a single year is nothing short of seismic.

Figure 8: Distribution of R&D companies by HQ country/region, 2018 and 2019



Source: Pharmaprojects®, January 2019

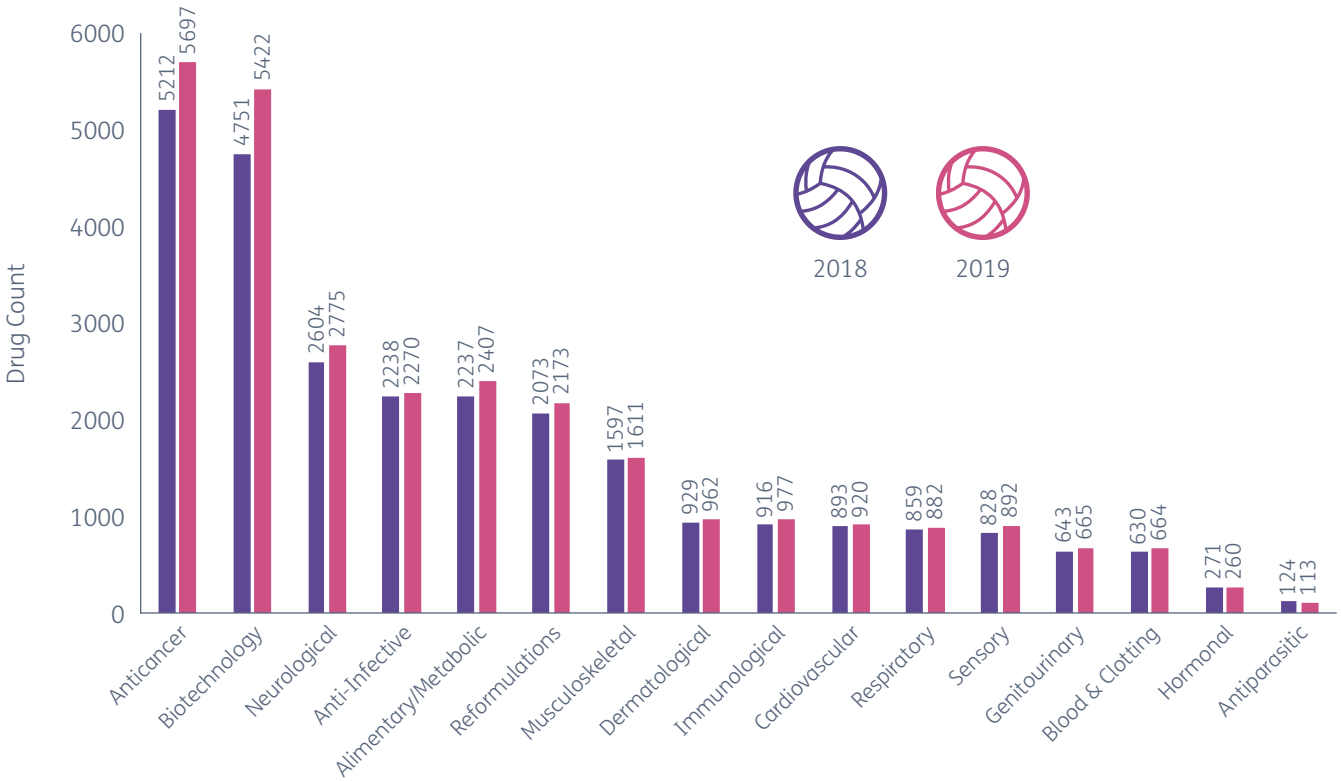
Top Therapies

A new champion and a great comeback

Let's change disciplines now and get the ball rolling on an examination of the pipeline by therapeutic area. The story here is forever the same – the dominance of cancer. This echoes many examples of people or teams dominating an era in the sporting world. In baseball, the New York Yankees played in 29 of the 44 World Series from 1921 to 1964, winning 20 of them. The West Indian cricket team, with its fearsome clutch of giant fast bowlers, was not beaten in a test series between March 1980 and May 1995, in a spell which included 20 series wins. AP McCoy had an incredible uninterrupted 20-year run as British Champion Jockey from 1996–2015. And currently enjoying a fresh period of superiority in the US National Basketball Association are the Golden State Warriors, who have won three championships in the last four years, and in 2016 they had the best regular season in NBA history with a record of 73-9. But the key point is that all of these periods of dominance have or will come to an end, being ultimately limited by the enforced retirement of key personnel. Cancer's pre-eminence as a therapeutic target, however, is showing all the signs of becoming as immortal as cancer cells themselves.

Figure 9 reveals that cancer increased its pipeline size by an average-busting 9.3% to 5,697 active drugs this year. This was once again the highest expansion rate of any of the true Therapeutic Areas. Biotechnological drugs, not really a Therapeutic Area but included in this analysis, did exceed that with double-digit growth of 14.1%, but it's worth noting that many drugs will be counted in both of these categories, as cancer therapies move the goalposts to capitalize on more targeted and biotech-based approaches.

Figure 9: The R&D pipeline by therapy group, 2018 and 2019

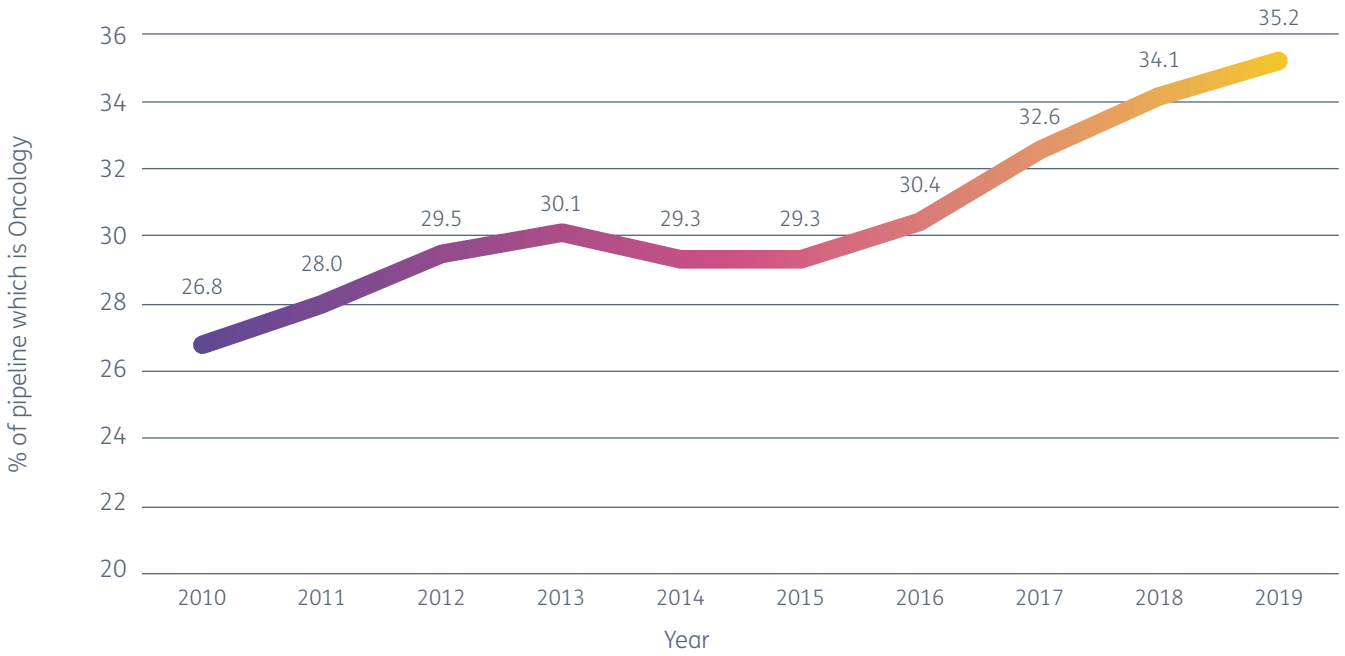


Source: Pharmaprojects®, January 2019

Further down the field, Neurologicals (+6.6%) and Alimentary/Metabolics (+7.6%) both knocked it out the park with higher than average increases, whereas, if you excuse the mixed metaphor, Anti-infectives (+1.4%) and Musculoskeletals (+0.9%) were both well below par. All but the tiniest two categories, Hormonal and Antiparasitic, did post some kind of increase though, in contrast to last year.

Just how much cancer is tightening its grip is emphasized by Figure 10, which shows how it is claiming an ever-larger proportion of R&D. In 2010, already more than a quarter of all drugs in development had a cancer indication, and this passed one in three last year. In 2019, we are looking at a further increase, to 35.2%. The danger here is that the industry begins to focus so much on oncology that it starts to harm other, equally deserving, therapeutic needs. How far can the pharma industry continue to shift resources into cancer before it becomes in danger of scoring an own goal?

Figure 10: Proportion of the pipeline which is in development for cancer, 2010–19



Source: Pharmaprojects®, January 2019

Breaking down the broad therapeutic areas into the more discrete subclasses of the 236 individual categories, we find, for the first time since we began these analyses back in 2003, a change at the top spot. Moving into pole position this year is the 'Anticancer, immunological' category, with a stadium-sized 16.5% increase in pipeline drugs. With this, it finally overhauls the more general and traditional 'Anticancer, other' class, which nonetheless saw a 3.2% expansion of its own. This really emphasizes just how much immunological approaches to treating cancer, such as the use of monoclonal antibodies, CAR-T cell therapies, and certain immuno-oncology techniques (see later) are taking over as the centre-forwards and captains of the attack on cancer.

Table 2: Top 25 therapeutic categories

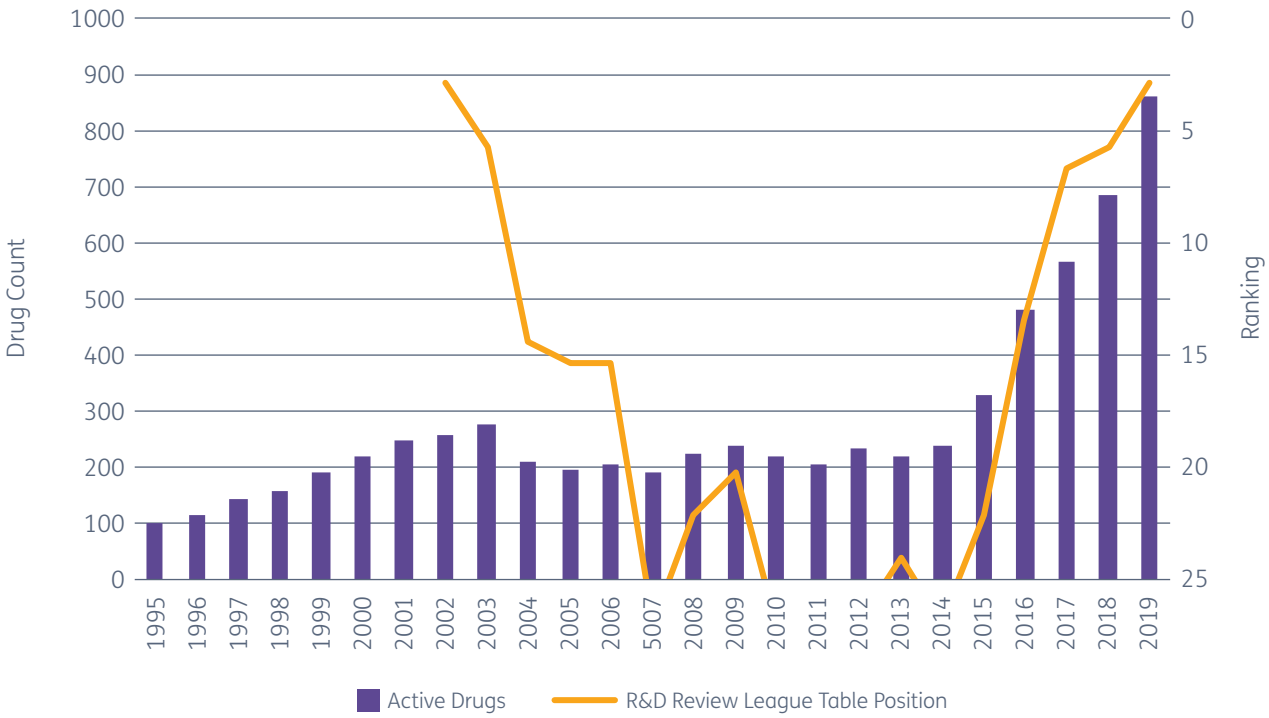
Position 2019 (2018)	Therapy	No of R&D products 2019 (2018)	Trend
1 (2)	Anticancer, immunological	2,731 (2,345)	↑
2 (1)	Anticancer, other	2,450 (2,374)	↑
3 (6)	Gene therapy	864 (633)	↑
4 (4)	Monoclonal antibody, other	818 (658)	↑
5 (3)	Prophylactic vaccine, anti-infective	702 (711)	↓
6 (5)	Ophthalmological, other	690 (637)	↑
7 (7)	Antidiabetic	571 (605)	↓
8 (9)	Neurological	567 (479)	↑
9 (10)	Immunosuppressant	511 (476)	↑
10 (8)	Anti-inflammatory	473 (487)	↓
11 (12)	Musculoskeletal	461 (444)	↔
12 (16)	Monoclonal antibody, human	461 (425)	↑
13 (13)	Cognition enhancer	459 (435)	↑
14 (14)	GI inflammatory/bowel disorders	459 (435)	↑
15 (17)	Monoclonal antibody, humanized	455 (418)	↑
16 (15)	Reformulation, fixed-dose combinations	446 (434)	↔
17 (11)	Antiviral, other	439 (459)	↓
18 (19)	Biosimilar	432 (408)	↑
19 (22)	Cardiovascular	412 (379)	↑
20 (23)	Reformulation, other	408 (364)	↑
21 (20)	Analgesic, other	390 (407)	↓
22 (-)	Metabolic and enzyme disorders	389 (-)	↑
23 (23)	Recombinant, other	389 (364)	↑
24 (-)	Neuroprotective	386 (-)	↑
25 (25)	Anticancer, vaccine	364 (323)	↑

Source: Pharmaprojects®, January 2019

Now there's nothing sport loves more than a great comeback, and such stories are legion. George Foreman reclaiming the world heavyweight boxing crown aged 45 years, after retiring a full 17 years previously. Tom Brady leading the New England Patriots to overcome a 25-point deficit in 2017's Super Bowl, defeating the Atlanta Falcons 34-28 in overtime. Dennis Taylor winning the 1985 World Snooker championship on the final black in the final frame after earlier being 8 frames to 0 down. More recently, Serena Williams returning from pregnancy and illness ranked at 181, only to reach her 10th Wimbledon singles final. And more controversially, and in perhaps the best example of a sports and pharma crossover (in more ways than one), cyclist Lance Armstrong winning seven Tour de France cycle races in a row after previously being given only a 40% chance of survival from his metastatic testicular cancer.

The big comeback in therapeutics is undoubtedly gene therapy, which this year rises to number three. With this, it equals its previous highest position in the league, way back in 2002 (when records of this metric were first recorded). Figure 11 illustrates its changing fortunes handsomely. The purple bars show its pipeline size going back as far as 1995, measured via the left-hand-side axis. After hitting three figures for the first time in 1996, gene therapy made steady advances to reach an early peak of 275 projects in 2003. It was then hit by setbacks in clinical trials and went into a decline; in fact, it wouldn't achieve these heights again until 2015. Since then, we have seen both the eventual coming to the market of 'traditional' gene therapies, such as Spark Therapeutics' aforementioned Luxturna (voretigene neparvovec), and the addition of therapies involving an element of ex vivo gene therapy such as CAR-T and CRISPR, which have sent this strategy into the stratosphere. The gold line tracks its position in the therapeutic category league table according to the right-hand-side axis, and neatly illustrates its journey from the dizzy heights of number three in 2003, to out of the Top 25 completely, and back up to number three again this year.

Figure 11: The rise and fall and rise of gene therapy



Note: tracking of Therapeutic Category league tables only began in 2002.

Source: Pharmaprojects®, January 2019

Elsewhere in the table, once again, the three categories of monoclonal antibody all make strong showings, with the general, human and humanized categories clocking up an extra 24.3%, 8.5% and 8.9%, respectively, onto the scoreboard. Anti-infective vaccines are thus pushed down two places to number five, while the most striking decline is in the Antidiabetic category. Despite retaining the number seven spot, the pipeline for this class of drugs shrank by 5.6%. Antivirals also fell on the back of further exits from the hepatitis C franchise.

All the trends in Table 2 are further amplified in Table 3, where we go down to the disease level. Breast cancer pulls further into the lead, with a 6.5% uptick, although runner-up non-small cell lung cancer has a bigger percentage rise (7.7%). Various cancers now account for 14 of the top 20 diseases, and of these, only prostate cancer at number eight and brain cancer at number nine have smaller pipelines this year than last year (the latter only declines by one drug anyway). This makes cancer dominate disease pipelines in the same way that China owns Olympic table tennis. Away from oncology, Alzheimer's disease battles on and up the table, but is still searching for that elusive victory. The hot newcomer to the team is non-alcoholic steatohepatitis, which debuts this year at number 21.

Table 3: Top 25 diseases/indications

Position 2019 (2018)	Disease*	No. of active drugs 2019 (2018)	Trend
1 (1)	Cancer, breast	774 (727)	↑
2 (2)	Cancer, lung, non-small cell	586 (544)	↑
3 (3)	Cancer, colorectal	535 (503)	↑
4 (4)	Cancer, ovarian	442 (434)	↔
5 (5)	Cancer, pancreatic	438 (430)	↔
6 (8)	Alzheimer's disease	405 (381)	↑
7 (6)	Diabetes, Type 2	382 (407)	↓
8 (7)	Cancer, prostate	366 (381)	↓
9 (9)	Cancer, brain	360 (361)	↔
10 (11)	Cancer, melanoma	357 (346)	↔
11 (12)	Cancer, leukaemia, acute myelogenous	338 (326)	↔
12 (10)	Arthritis, rheumatoid	335 (352)	↓
13 (17)	Cancer, myeloma	283 (254)	↑
14 (15)	Cancer, head and neck	283 (258)	↑
15 (19)	Cancer, gastrointestinal, stomach	276 (242)	↑
16 (13)	Cancer, liver	273 (272)	↔
17 (18)	Parkinson's disease	271 (252)	↑
18 (14)	Pain, nociceptive, general	266 (262)	↔
19 (16)	Psoriasis	260 (256)	↔
20 (22)	Cancer, lymphoma, non-Hodgkin's	231 (215)	↔
21 (-)	Non-alcoholic steatohepatitis	222 (-)	↑

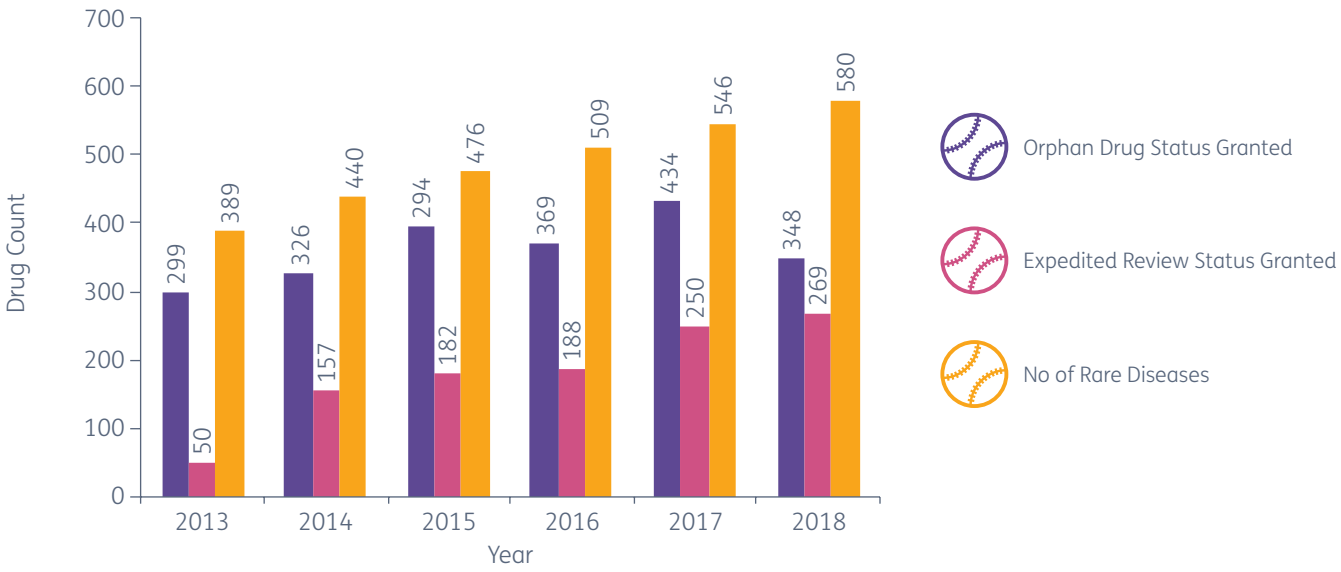
22 (21)	Cancer, renal	221 (218)	↔
23 (20)	Asthma	196 (224)	↓
24 (25)	Infection, HIV/AIDS	189 (177)	↔
25 (-)	Cancer, bladder	179 (-)	↑

**Excludes the more generalized indications which include the term 'unspecified' to focus in solely on counting drugs where precise target diseases have been identified.*

Source: Pharmaprojects®, January 2019

A further trend which is not reflected in the table of top diseases is the oft-trumpeted focus on rare diseases. Like some of those Olympic sports which you never realized were actually in the Olympics –dressage, artistic swimming, Greco-Roman wrestling, or skeleton, anyone? – you may not have heard of them, but they are very important to those involved. And increasingly, they are seen by the pharma industry as a potentially lucrative option, since they can command high prices. In Figure 12, we can see how the number of rare diseases being investigated by the pharma industry has shown a significant increase: up from 389 at the end of 2013 to 580 five years later. [A rare disease is defined as one with a prevalence of 1 in 2,000 people in the EU, or affecting fewer than 200,000 people in the US (equivalent to around 1 in 1,600 people)]. The total number of drugs in development for rare diseases has similarly grown from 4,615 in 2018 to 4,953 now. Regulatory authorities continue to offer incentives to encourage such developments. The number of expedited review designations (eg breakthrough therapy, accelerated approval) being granted continues to grow to record levels, and the number of orphan drug designations granted remains high.

Figure 12: Rise in numbers of drugs receiving Orphan Drug status or an Expedited Review designation*, and the number of rare diseases under investigation, 2013–18



**Data for 2013 not complete as we only began systematically recording the dates of these events mid-year.*

Source: Pharmaprojects®, January 2019

Mechanisms and Targets

Immuno-oncology completes rookie's rapid rise

Sometimes, sports superstars can seem to come from nowhere. Ex-England cricket captain and all-time highest run-scorer for his country, Sir Alastair Cook, was knighted in this year's New Year Honours List, but few outside of county cricket had heard of him when he was first called up to play for his country as a last-minute replacement, aged 21. He scored a century (100 runs) on his debut against India, and followed this up with centuries in his first matches against Pakistan, West Indies and Bangladesh. He scored over 1,000 runs in his first season as an international cricketer – a truly stellar arrival. There's a similar story to be told about Nick Foles, the backup quarterback for the Philadelphia Eagles, an American football team. In 2017, after the starting quarterback tore his anterior cruciate ligament late in the season, Foles had to step in and lead the team as the playoffs approached. He led them on a magical run through the playoffs (the Eagles were underdogs in every game of the playoffs), capped off by a win over the New England Patriots in the Super Bowl. Foles was named Super Bowl Most Valuable Player 2018.

Our league table of the most popular mechanisms of action (MOA) this year (Table 4) follows the therapeutic categories table in also having a new number one for the first time ever, but in this case, it's a real rookie taking the top spot. The Immuno-oncology (IO) therapy category was only added to Pharmaprojects in January 2015, to aid easy identification of drugs using an emerging new way of treating cancer – mobilizing the body's immune system to identify and to attack its cancer cells, rather than using drugs directly acting against the tumour. The category entered the 2016 MOA chart already at number two, and this year finally ascends to the top of the medals podium. Strikingly, of the 1,875 drugs reported to be in development which use this strategy, only 1.6% have so far reached at least the pre-registration phase, with just 24 drugs (1.3%) actually marketed to date. That's one huge leap of faith (worthy of Mike Powell, who has held the world long jump record for almost 30 years).

Table 4: Top 25 mechanisms of action (pharmacologies)

Position 2019 (2018)	Mechanism of action (pharmacology)	No. of active drugs 2019 (2018)	% of compounds PR/R/L
1 (2)	Immuno-oncology therapy	1,875 (1,332)	1.6
2 (1)	Immunostimulant	1,387 (1,501)	10.2
3 (11)	T-cell stimulant	404 (106)	1.7
4 (3)	Immune checkpoint inhibitor	327 (211)	3.7
5 (4)	Immunosuppressant	199 (208)	30.7
6 (5)	Angiogenesis inhibitor	186 (169)	17.7
7 (6)	Vascular endothelial growth factor (VEGF) receptor antagonist	149 (138)	14.8
8 (7)	Apoptosis stimulant	131 (116)	15.3
9 (10)	Radiopharmaceutical	122 (108)	8.2
10 (9)	Opioid mu receptor agonist	116 (110)	37.9

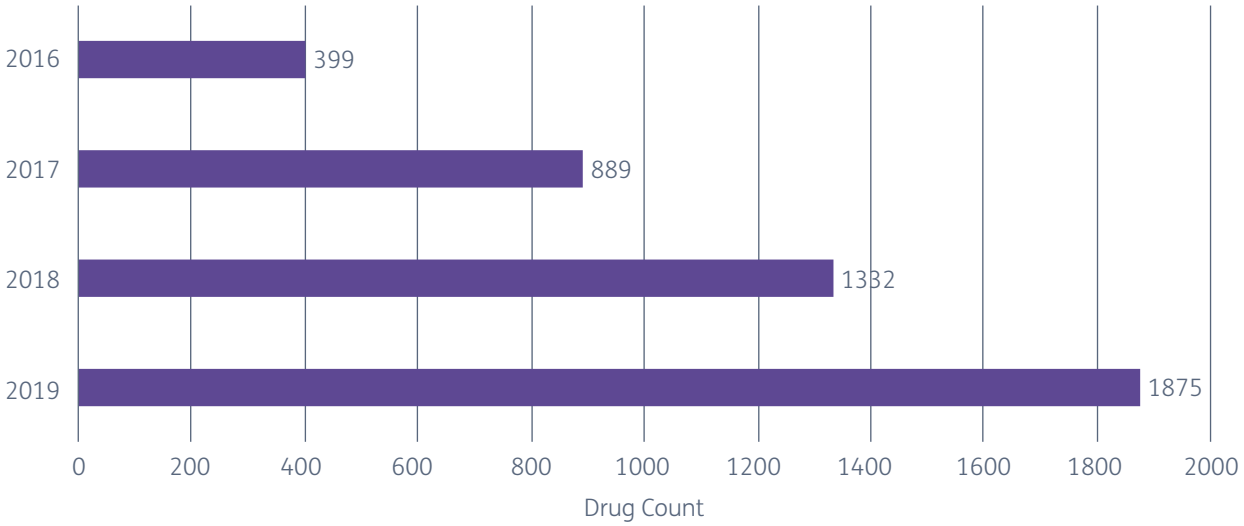
11 (12)	Tumour necrosis factor alpha antagonist	107 (102)	30.8
12 (8)	DNA inhibitor	106 (111)	23.6
13 (13)	Cyclooxygenase 2 inhibitor	103 (93)	33
14 (22)	Immune checkpoint stimulant	99 (63)	0
15 (15)	ErbB-2 antagonist	91 (82)	12.1
16 (14)	Glucocorticoid agonist	88 (88)	43.2
17 (-)	Glucagon-like peptide 1 receptor agonist	88 (-)	12.5
18 (-)	PD-1 antagonist	83 (-)	7.2
19 (17)	Gene expression inhibitor	81 (78)	1.2
20 (18)	Cell wall synthesis inhibitor	77 (70)	31.2
21 (-)	PD-L1 antagonist	74 (-)	4.1
22 (13)	Cyclooxygenase 1 inhibitor	72 (93)	36.1
23 (20)	Microbiome modulator, live microorganisms	70 (66)	0
24 (21)	Insulin secretagogue	67 (64)	49.3
25 (-)	CD20 antagonist	64 (-)	29.7

Abbreviations used in table: PR = pre-registration; R = registered; L = launched

Source: Pharmaprojects®, January 2019

Just how rapid the rise of immuno-oncology has been can be seen in Figure 13. After hitting nearly 399 drugs in its first 12 months of existence, it saw a 123% expansion during its sophomore year, while this year it has added more drugs than ever to its total, with an extra 543 drugs being added to its portfolio.

Figure 13: The rise of immuno-oncology as a therapeutic strategy



Source: Pharmaprojects®, January 2019

Of course, the mechanism of action classification used in Pharmaprojects is both hierarchical and also includes such useful 'catch-all' categories like the immuno-oncology term. This, added to the fact that a drug's precise mode of action may not be disclosed or even identified during the earliest stages of development, means that the higher level, broader categories are naturally favoured in the chart, often only later replaced with more precise MOAs. Eight of the top 10 could be said to fall into this category, with one of these a new entry also related to immuno-oncology: T-cell stimulant. This is applied to CAR-T cell therapies, and to some small molecules affecting proteins which regulate T-cell activity in the immuno-oncology space, and also to some vaccines known to specifically induce T-cells. With another IO-related category at number four in only its second year (Immune checkpoint inhibitor), and Immune checkpoint stimulants the highest climber within the Top 25, it looks as if immuno-oncology is taking over (Table 4).

But it's actually further down the table where we get the best sense of how all-pervasive this strategy is becoming, as, for the first time, categories pertaining to individual protein targets in the IO universe appear. New at number 18 is PD-1 antagonist, and at number 21, we see PD-L1 antagonist debuting. Both of these categories have successfully delivered drugs to the market, in the shape of Opdivo (nivolumab), Keytruda (pembrolizumab) and, new in 2018, Libtayo (cemiplimab) for PD-1, and Tecentriq (atezolizumab), Bavencio (avelumab) and Imfinzi (durvalumab) for PD-L1. However, the highest new entry was the diabetes-related category Glucagon-like peptide 1 receptor agonist at number 17 – proving that there's still life outside of immuno-oncology (Table 4).

A better indication of the diversity of drug R&D is perhaps to be drawn from Table 5, where we find the Top 25 physiological proteins targeted by drugs. Here, there's no change at the top, with the mu1 opioid receptor still winning by a nose in the race to be the most common target for drug development (either agonized to treat pain or antagonized for opioid-induced constipation). It will need to keep its eye on the ball if it is to retain its crown though, as the breast cancer target HER-2 is snapping at its heels in the runner-up position. As well as pain, constipation and cancer, the Top 10 includes targets relevant in the treatment of inflammatory diseases and diabetes.

Table 5: Top 25 drug protein targets

Position 2019 (2018)	Target	No. of active compounds 2019 (2018)	Trend
1 (1)	opioid receptor, mu 1	147 (140)	↑
2 (2)	erb-b2 receptor tyrosine kinase 2 [HER-2]	135 (120)	↑
3 (3)	vascular endothelial growth factor A	131 (119)	↑
4 (5)	tumour necrosis factor	123 (113)	↑
5 (7)	epidermal growth factor receptor	121 (107)	↑
6 (4)	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	113 (113)	↔
7 (6)	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) [COX-2]	112 (107)	↔
8 (8)	insulin receptor	104 (99)	↔
9 (10)	glucagon-like peptide 1 receptor	94 (80)	↑
10 (9)	opioid receptor, kappa 1	91 (88)	↔
11 (15)	CD19 molecule	86 (62)	↑
12 (17)	programmed cell death 1	86 (61)	↑
13 (12)	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) [COX-1]	79 (71)	↑
14 (18)	CD274 molecule	76 (57)	↑
15 (-)	CD3e molecule, epsilon (CD3-TCR complex) [CD3]	76 (-)	↑
16 (11)	dopamine receptor D2	74 (73)	↔
17 (13)	gag-pol, HIV-1	73 (64)	↑
18 (14)	membrane-spanning 4-domains, subfamily A, member 1 [CD20]	72 (64)	↑
19 (19)	estrogen receptor 1	62 (57)	↔
20 (20)	adrenoceptor beta 2, surface	59 (57)	↔
21 (21)	androgen receptor	57 (56)	↔
22 (22)	amyloid beta (A4) precursor protein	55 (53)	↔
23 (23)	kinase insert domain receptor	55 (53)	↔
24 (-)	mechanistic target of rapamycin (serine/threonine kinase)	53 (-)	↑
25 (16)	tubulin, beta class I	52 (62)	↓

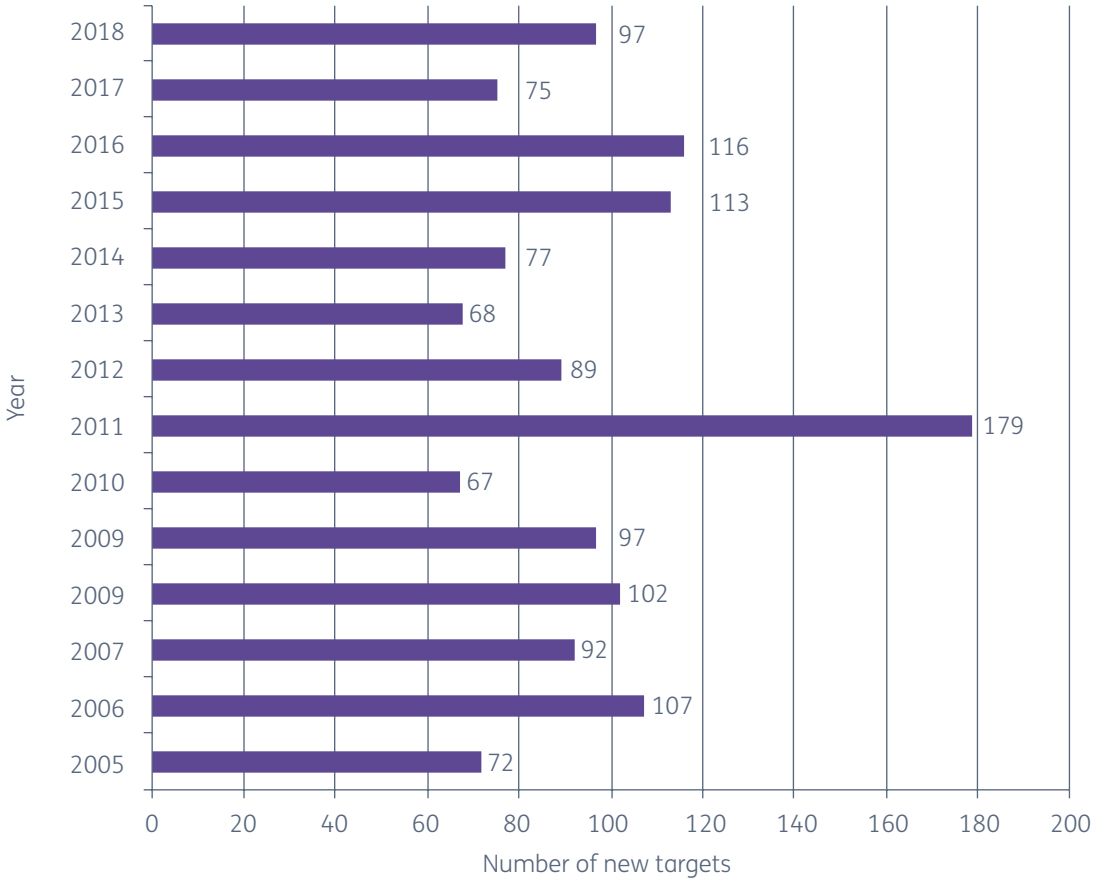
Note: NCBI names are used, except for additions in italics made by us for clarity.

Source: Pharmaprojects®, January 2019

Here too, immuno-oncology is stepping up to the plate. No individual IO target has quite made it to the first team yet, but outside of the Top 10 there are several players pressing for a place. CD19 is leading the pack at number 11, with PD-1 at number 12 and CD274 (better known as PD-L1) at 14, all of which are expanding their pipelines. The highest new entry also falls into this space at number 15: CD3, which activates both the cytotoxic T-cell (CD8+ naive T-cells) and also T-helper cells (CD4+ naive T-cells).

It was a pretty decent year in terms of numbers of newly discovered targets, as evidenced by Figure 14. This shows that 97 protein targets were added to the therapeutic pantheon during 2018 – bang on the mean seen over the past 14 years, and an improvement on the 2017 number of 75. In another positive sign, the total number of targets which drugs are currently being actively developed against rose this year, after falling in 2018. It now stands at 1,706, up from 1,657.

Figure 14: Number of new drug protein targets identified by Pharmaprojects, by year



Source: Pharmaprojects®, January 2019

Types of Pipeline Drugs

Four out of every 10 drugs are now biologicals

Pharma R&D, like sports, continues to evolve over time. For both, there is a strong need to become ever better at driving this development. In sports, general levels of fitness have increased. The days of athletes enjoying a 40-a-day habit and a few pints with whiskey chasers at the 19th hole are pretty much over. Nowadays, a healthy lifestyle is a prerequisite for even some of the less physical sports, along with physiotherapy, nutritional rigour, and sports psychology. The cost of a physical breakdown in a multimillion-dollar professional sporting world can be enormous – just ask tennis star Andy Murray.

The big long-term evolving trend in pharma over the past couple of decades has been the move away from traditional small-molecule drugs towards biotech-centred strategies. Often, such as with the use of monoclonal antibodies, such an approach can lead to a better-targeted therapy. However, balanced against that are the facts that such approaches are generally more expensive, and that most biologicals cannot be given orally. So, what's the state of play in the tussle between traditional and biotech drug development in 2019?

Table 6 shows how these changes are reflected via Pharmaprojects' Origin of Material field – a data point which describes how a drug was originally produced. This shows that small-molecule synthetic chemistry is still the popular strategy, with 51% of the pipeline being derived this way. The number of drugs in development produced like this grew this year too, albeit only by 3.7%. Contrast this with antibody drugs at number two in the table. Although they only account for 12.7% of drugs, their numbers increased by 12.8%. Meanwhile, cell therapies at number five and virally delivered gene therapies at number seven posted pipeline expansions of 22.5% and 16.0%, respectively. This suggests that the move into biotechnology-derived drugs is gathering pace.

Table 6: Top 25 origins of pipeline drugs

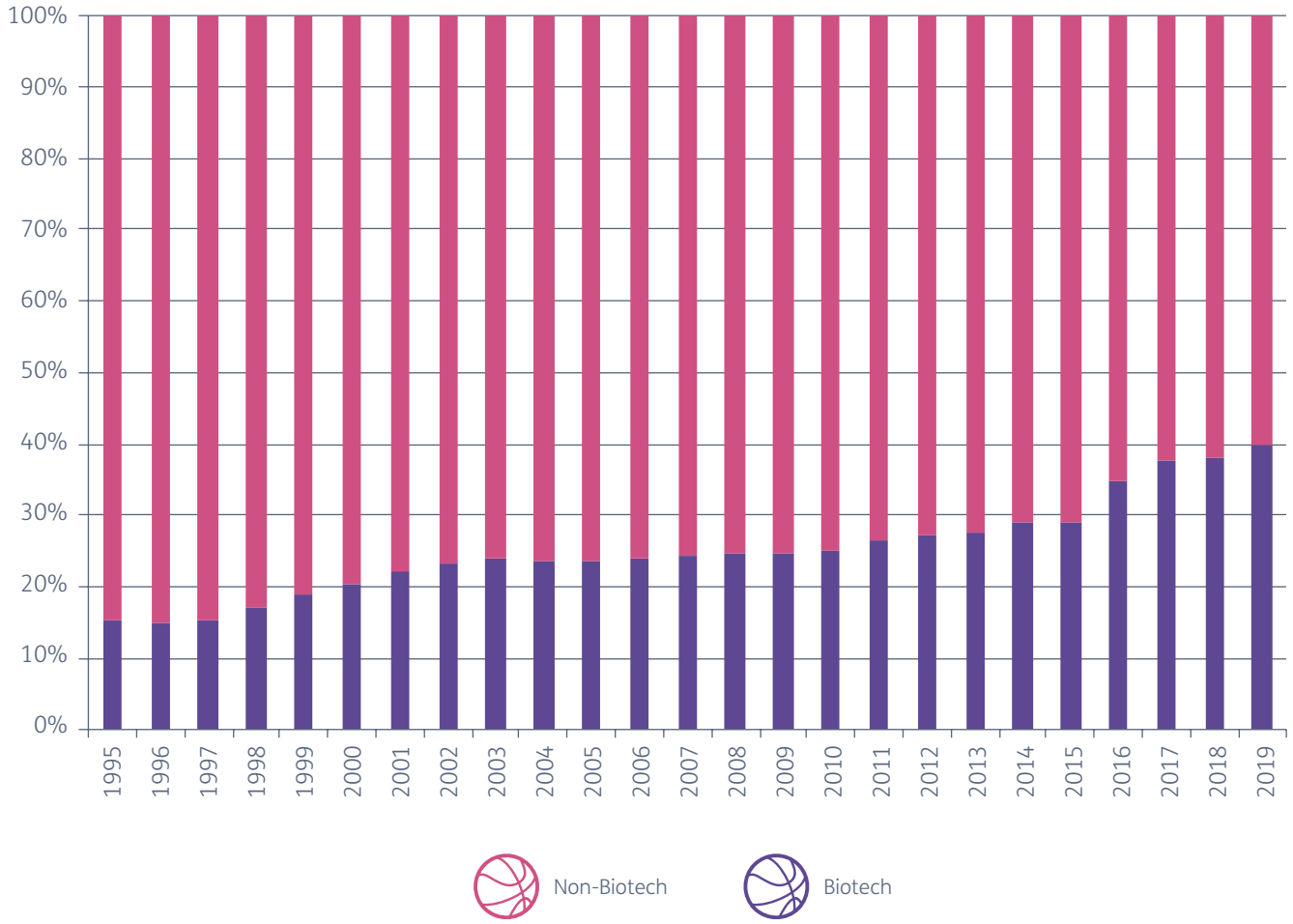
Position 2019 (2018)	Origin	No. of active products 2019 (2018)	Trend
1 (1)	Chemical, synthetic	8,285 (7,992)	↑
2 (2)	Biological, protein, antibody	2,041 (1,809)	↑
3 (3)	Biological, protein, recombinant	840 (826)	↔
4 (4)	Biological, protein	520 (508)	↔
5 (6)	Biological, cellular	512 (418)	↑
6 (5)	Chemical, synthetic, peptide	428 (438)	↓
7 (7)	Biological, nucleic acid, viral vector	407 (351)	↑
8 (9)	Chemical, synthetic, nucleic acid	392 (338)	↑
9 (8)	Biological, virus particles	373 (350)	↔
10 (10)	Biological, cellular, autologous	340 (304)	↑
11 (11)	Natural product, plant	266 (248)	↔
12 (12)	Biological, peptide	248 (231)	↔

13 (13)	Biological	221 (187)	↑
14 (15)	Biological, cellular, heterologous	167 (147)	↑
15 (17)	Biological, bacterial cells	162 (129)	↑
16 (14)	Biological, nucleic acid	161 (151)	↔
17 (16)	Biological, peptide, recombinant	147 (133)	↑
18 (18)	Biological, other	106 (128)	↓
19 (19)	Biological, nucleic acid, non-viral vector	102 (112)	↓
20 (20)	Chemical, semisynthetic	59 (57)	↔
21 (22)	Natural product	45 (45)	↔
22 (21)	Natural product, bacterial	43 (51)	↓
23 (23)	Natural product, animal	35 (30)	↑
24 (24)	Natural product, fungal	27 (28)	↔
25 (-)	Natural product, other	24 (-)	↑

Source: Pharmaprojects®, January 2019

This gradual but determined shift can be better observed by zooming out from Table 6 to look at the pipeline split simply along biotech/non-biotech lines, as in Figure 15. This shows how there has been a fundamental shift in approach over the past 20 years or so. Whereas biotech accounted for just 15% of the pipeline back in 1995, by 2019 this has reached 39.7%. That means that fully four in every 10 drugs under development are now biotech-derived. The proportion rose again this year, up from 37.9% in 2018, indicating that this realignment is not over yet.

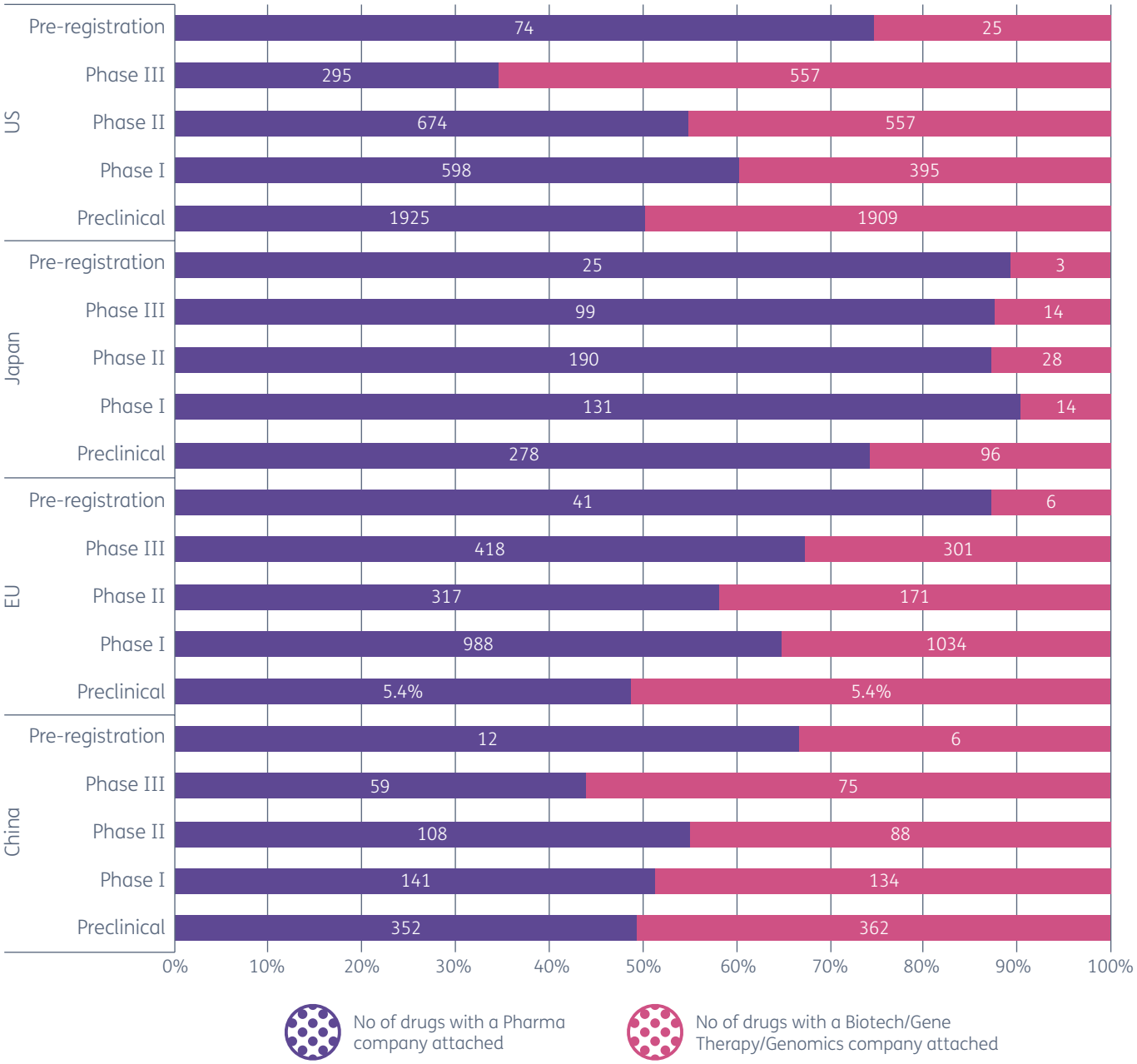
Figure 15: Biological versus non-biological drugs as a percentage of the pipeline, 1995–2019



Source: Pharmaprojects®, January 2019

Within this 60:40 split though, there are some interesting variations by geography and phase of development. In Figure 16, we analyzed drugs at five global development stages, from preclinical, through the various stages of clinical development, up to pre-registration. We looked at how many of these drugs were in development by traditional pharma companies, and how many were attached to biotech, gene therapy or genomics companies (note some drugs may be associated with both). Lastly, we broke that down by company headquarters into four market areas: China, the EU, Japan, and the US. Some quite striking differences emerged. The most biotech-heavy combination was Phase III drugs in the US, where the majority of candidates were associated with a biotech company. Contrast that with Japan, which across all phases has much more limited biotech company involvement – probably because it's more unusual for a Japanese company to describe itself in these terms. Perhaps surprisingly, China has the most consistent weighting towards biotech across the developmental course. These figures certainly show that there are marked differences in the penetration of biotech drugs across varying phases and markets.

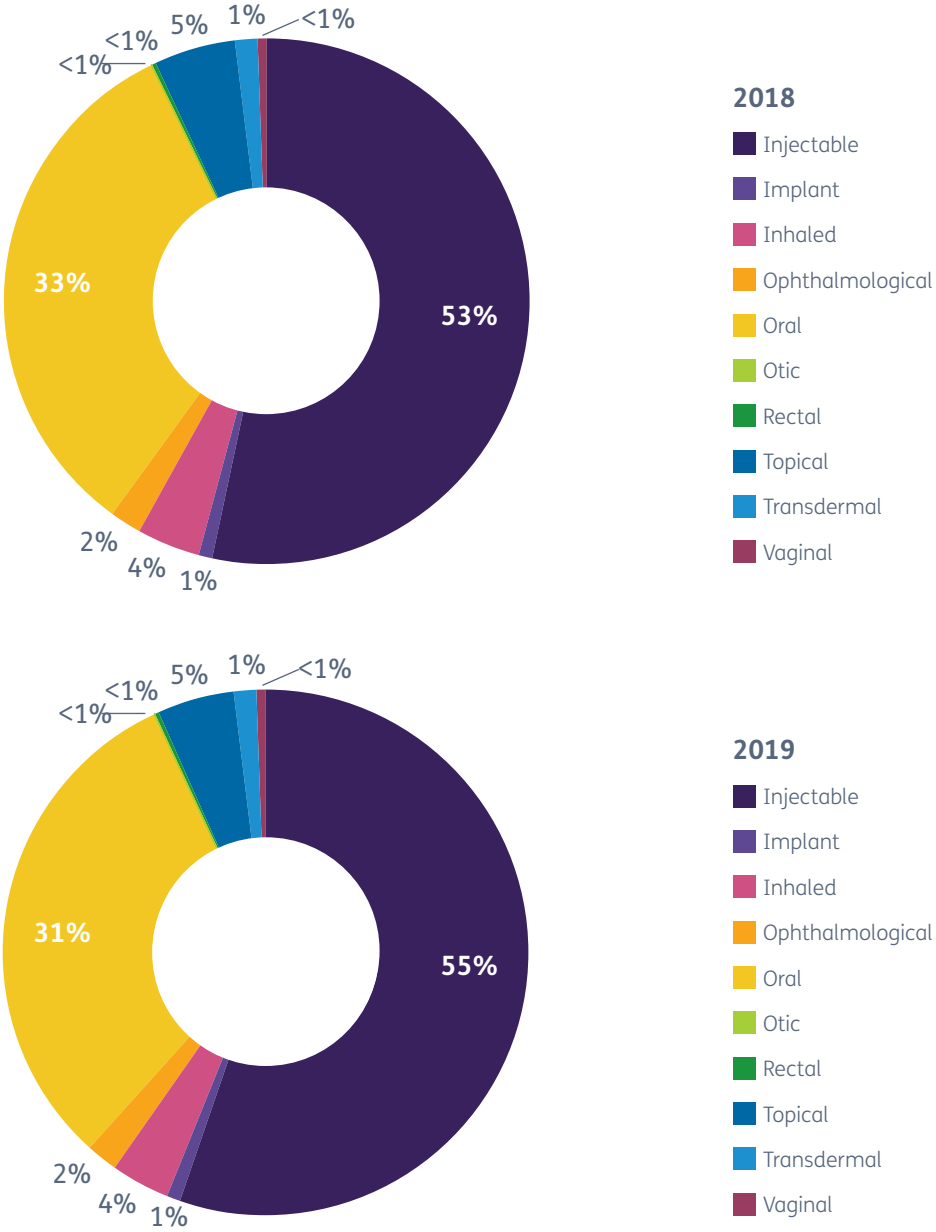
Figure 16: Pharma/Biotech company split of the pipeline, by phase and geography



Source: Pharmaprojects®, January 2019

With a greater proportion of biologicals in development this year, it's no surprise that the percentage of drugs delivered by the injectable route increased too. As Figure 17 confirms, the proportion of drugs in the pipeline requiring parenteral administration rose from 53% to 55%, with a concomitant fall in oral drugs from 33% to 31%. All other categories remained unchanged. This provides further evidence that biotech drugs are frequently regarded as sufficiently more efficacious, such that patients will be prepared to put up with a less pleasant and convenient route of administration.

Figure 17: Pipeline by delivery route, 2018 and 2019



Source: Pharmaprojects®, January 2019

A Satisfactory Season, as Pharma Picks up the Pace

So, as the 2019 pharma season kicks off, how is the squad feeling when it reflects on its performance over the past 12 months? Is it over the moon, or sick as a parrot? Could it be said to be landing more knockout blows, or is it on the ropes? Is the team overdue a clear-out, or finally gelling to become a force to be reckoned with? Is pharma more Michael Phelps (the most successful Olympian ever), or Eddie 'The Eagle' Edwards? [For those not in the UK, the latter was Britain's first Olympic ski-jumper to compete in 60 years, participating in the 1988 winter games. He came last in both of his events, and became something of a byword for haplessness, although was admittedly seen as a bit of a folk hero too by us self-deprecating Brits].

As an industry commentator, I would sum up the season as 'satisfactory'. We have had a number of years now where pharma has delivered a decent return on investment in terms of new drug launches. The trophy cabinet may not be exactly bulging yet, but there's sufficient success to stave off sacking the manager for now. Just as in sport, at the end of the day, how you played matters much less if you get the right results. The own-goal of a Phase II failure looks much less galling in the event of an ultimate victory. And we can stomach spending more on the R&D of the squad's salaries if at least one member ends up wearing the yellow jersey or the green jacket.

Even more so than last year, it's worth noting how the wider context of world events could yet make pharma fall off its proverbial bike. At the time of writing, the UK, and by extension the rest of the EU, is currently continuing to convulse over the self-inflicted and potentially career-ending injury that is Brexit. As things stand, Britain could yet crash out of the EU deal-less, wrecking its own economy and likely causing currency instability worldwide. Meanwhile, the US government remains effectively closed as the Mexican standoff over the border wall continues. Russia, China and the Middle East all remain unpredictable, and global trade wars lurk in the background. The sense that one questionable decision from the referee could spark serious crowd trouble is never very far away.

Sports such as soccer may have less of a hooligan issue than they did 40 years ago, but in pharma, one issue still gets the angry mob chanting – drug pricing. There might seem to have been less sound and fury in the past 12 months, but the issue – and its attractiveness to populist politicians – has not gone away. Pharma chiefs at the recent J.P. Morgan conference in San Francisco were keen to head off the oncoming storm of new policies to curb drug pricing by stressing the value of innovation. Regeneron's President, George Yancopoulos, quoted in Scrip, said: *"Yes, there are bad players. Yes, there are pricing problems. Yes, there are cost issues in all this, but we need innovation, and we have to protect it. Whatever solutions are put in place, there is nothing more important to our future as a society and as human beings than to continue supporting and, in fact, increase the incentives for innovation."*[2] But, just as many fans baulk at the annual earnings of athletes, the top three of which (boxer Floyd Mayweather and footballers Lionel Messi and Cristiano Ronaldo) each earned eyerolling amounts of over $100m a year in the latest figures, the public may find the $1m-plus cost of gene therapies hard to stomach. A continued backlash could yet provide pharma with a whole set of extra hurdles to overcome.

2. Scrip (2019) J.P. Morgan 2019: Industry Throws A Bonanza, With An Elephant In The Room. Available from: https://scrip.pharmaintelligence.informa.com/SC124466/JP-Morgan-2019-Industry-Throws-A-Bonanza-With-An-Elephant-In-The-Room [Accessed 17 January 2019].

As more players join the scrum that is immuno-oncology, it's also worth reminding ourselves that many of these innovations will only be applicable to a small number of people in first-world countries. Whether or not the latest CAR-T therapy is approved is likely to be low down on the concerns of a sub-Saharan African who doesn't have clean drinking water or a mosquito net for the night. Infectious disease tends to be relegated from much of the industry's premier priorities, but is still a daily fact of life for billions. Meanwhile, pressure on healthcare system budgets is likely to come from the Western obesity crisis as much as it is from high-cost niche drugs. And the effects of global warming could yet turn out to be the biggest threat of all. It's often said that there is a price to be paid if you want to become an elite athlete. Many train all day every day, have strict diets, and may sacrifice education and personal lives to focus on a singular goal. It's important that the pharma industry doesn't become too myopic and lose track of the bigger picture in pursuit of that single Olympic gold medal. And it needs to be a team player always, working at all times with governments, payers, and above all, patients.

So, 2019 sees the pharma industry squad marching forward with some great scores, and plenty of points on the board, but with a few ongoing niggling injury concerns. Its fans remain engaged, but worried that ticket prices look to be continuing to climb. As commentators on the industry, we try to avoid some of the more famous sporting gaffes, although this hilarious one from former England soccer manager Ron Atkinson does seem apposite: *"I'm going to make a prediction – it could go either way."* At least pharma is unlikely to ever produce a dull 0-0 draw. It's an endless, fascinating and engrossing competition, and we at Pharmaprojects will always be cheering loudly from the stands, while at the same time diligently updating our formbooks.

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