Pharma Intelligence
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Pharma R&D Annual Review 2020

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Introduction

Welcome to Pharmaprojects' 2020 review of trends in pharmaceutical R&D. For almost 30 years now, I've been taking an annual look at the evolution of pharma R&D, and in this whitepaper, I'll look at the state of play at the start of 2020. We'll assess industry trends by examining the pipeline by company, therapeutic area, disease, target and drug type, using data from Informa Pharma Intelligence's Pharmaprojects, part of the Citeline suite of products, which has been tracking global drug development since 1980. This year, improvements in our data granularity have permitted a feast of new analyses too, so we'll be digging into the pipeline more deeply than ever. 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 sampling a veritable banquet of different data points, to get a flavour of where R&D is heading as we move into an exciting new decade.

Regular readers of this report (which has been running since 1993) will know that in recent years, I've threaded a different theme through each edition, to highlight points, to draw analogies, and to inject a little spice into what could otherwise be a rather thin gruel of statistics, charts and tables. Topics selected so far have included astronomy, movies, the natural world, music, and, last year, sport. This year – if you haven't already guessed – I've picked a food and drink motif. It seems apposite, since the two commodities which all of us need to ingest to stay alive are meals and medicines – increasingly, we might even need to take the latter to counteract the effects of too much of the former. Both are subject to regulation – in the US, by the same body (the FDA). Both are of course huge, international industries, dominated by gigantic conglomerates, but augmented by many more tiny niche players. And while both nutrition and therapeutics should be available to all as a basic human right, the difference in access to both for the rich compared to the poor remains shameful. It also seemed an appropriate topic to focus on writing as I am from the UK, a country where, bizarrely, the top-rated TV programme of all is a show about making cakes *(The Great British Bake Off)!*

The food and pharma industries are also similarly uber-competitive. A glance at a list of the world's best restaurants at the start of the last decade reveals that only two, Mirazur on France's Côte d'Azur, and Copenhagen's Noma, remain in the top 10 today. While 2010's number one Noma is at number two now, the 2010 runners-up, Spain's El Bulli and the UK's The Fat Duck, aren't even in the 2019 top 50. The former actually closed in 2011, while the latter may have just gone out of fashion – its chef, Heston Blumenthal, was a high-profile TV chef briefly, famed for his 'molecular chemistry' approach to cooking and certain eyebrow-raising delicacies, such as egg and bacon ice cream and snail porridge. Similarly, some of the recipes for drug development have fallen out of favour, and the menu of the top 10 mechanisms of action in particular would be very unfamiliar to someone observing from 2010. That being said, it's surprising how many of the top 10 companies are ostensibly the same. For many of these though, that may be in name only. Their structure, organization, R&D portfolios, and their head chef CEOs are mostly markedly different. However, food fads are notoriously fickle. Few at the turn of

the century would have heard of the superfood du jour quinoa; but then again, few would have heard of immuno-oncology either!

Like drugs, food can take many years to prepare, only to be ingested quickly with an expected swift and satisfying outcome. That £500/kg 40-day aged Wagyu beef isn't so expensive just because of the long aging process the meat undergoes; the cows had to be reared for three years on a luxurious diet and according to specific rules, just as drugs have to undergo a long and strictly regulated clinical trial programme. Even something as common-or-garden as an apple tree can take up to 10 years to begin producing fruit. Also, it certainly has seemed that the pharma industry in recent years is increasingly focusing on the Michelin-starred end of the market. Drugs for rare diseases command high prices just as prized foodstuffs such as rare truffles do. As we'll see, this concentration on the niche end of the pharma menu shows no signs of abating, and the industry must not lose sight of the more meat and potatoes varieties of drugs in its race for exclusivity.

So, to our main meal, the report. Not to over-egg the pudding, but the Pharma R&D Report feels particularly noteworthy this year, as 2020 marks Pharmaprojects' fortieth year as the leading intelligence service tracking pharmaceutical R&D. But before we tuck into our birthday cake in May, we began this year in January serving up our data according to a brand new and improved recipe. We introduced a new, more granular way of presenting and searching our data which explicitly links each unique drug programme's developing company, disease, country, and status. As with cooking, you don't just need the finest ingredients, you need to be able to combine them in the right way. This enhancement has given both us and our subscribers access to a whole smorgasbord of new data analyses, some of which we'll be able to use in this report. We'll be able to dissect the pipeline even more precisely and pull out ever more nuanced trends, just as the fine dining connoisseur can detect every distinct herb and spice in a well-prepared dish. Having just returned from a vacation in Thailand myself, a country which in my opinion has one of the finest cuisines in the world, my taste buds are still zinging with the flavours of green curries, phat kaphrao, and laap. Our new data structure this year will enable us to extract how the essence of pharma R&D similarly varies from country to country.

The number of analyses that you can do with Pharmaprojects would run into the millions, so it's perhaps best to view this report as a 'tasting menu'. Over a number of courses, we'll give a few mouth-watering selections of how we can slice our data by phase, company, disease, mechanism/target and type of drug, but our full carte is as long as are the many ways in which you can combine our multitudinous ingredients. The good news is though, you've got a reservation at the top table, and our chef-style analysts have been busy in the kitchen cooking up a storm. So, settle down, tuck in your napkin, and select a fine wine, as we guide you through our specially selected spread of pharma R&D trends, from soup to nuts!

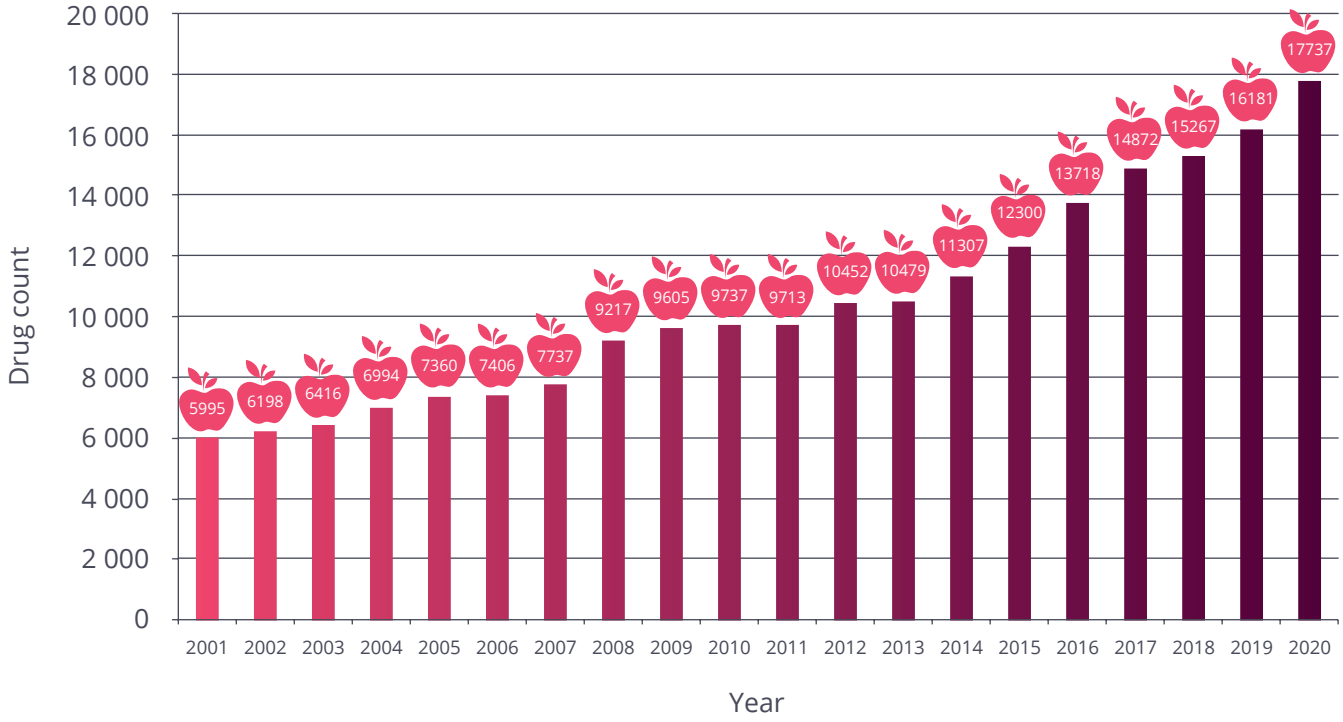
Aperitif – Total Pipeline Size

Nearly double-digit growth, as pharma piles on the weight

Let us whet your appetite by going straight in with a mouth-watering aperitif – 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. As ever, a caveat, much like an allergy-advice warning advice that comes with a meal: may contain data affected by internal changes in editorial practices. With our focus on delivering the new drug programme landscape enhancements, we may have been slightly less zealous than usual in moving drugs whose activity appears to have lapsed over to the 'No development reported' status. This might have had a small but significant effect in moving all analyses here, which are restricted to active drugs, upwards. But this effect will be across the board (it won't favour particular diseases or companies, for example), so won't affect the trends seen in subsequent sections, and it certainly could only account for a small part of the increase in the overall pipeline size, because this year, that's enormous.

As Figure 1 shows, not only has the overall size of the pipeline increased yet again, to 17,737 drugs, but the growth rate has also shot up, to 9.62% this year. That's almost double-digit growth, and much bigger than 2019's 5.99% and 2018's 2.66% expansion rates. This means that there are 1,556 more drugs in development than there were at this time last year – the biggest increase ever. And to prove that this rise isn't just purely down to drugs not being removed from the count due to inactivity, we can point to a big increase in the number of brand-new drugs entering the count. There were 4,730 new drugs added to the Pharmaprojects database during 2019, much more than the 4,001 added during 2018. Is this better detection on our part, more robust disclosure on the industry's part, or a bit of both? Or is it that there are just more drugs in development? And should we be raising a glass to this, or not?

Figure 1: Total R&D pipeline size, by year, 2001–2020



Source: Pharmaprojects®, January 2020

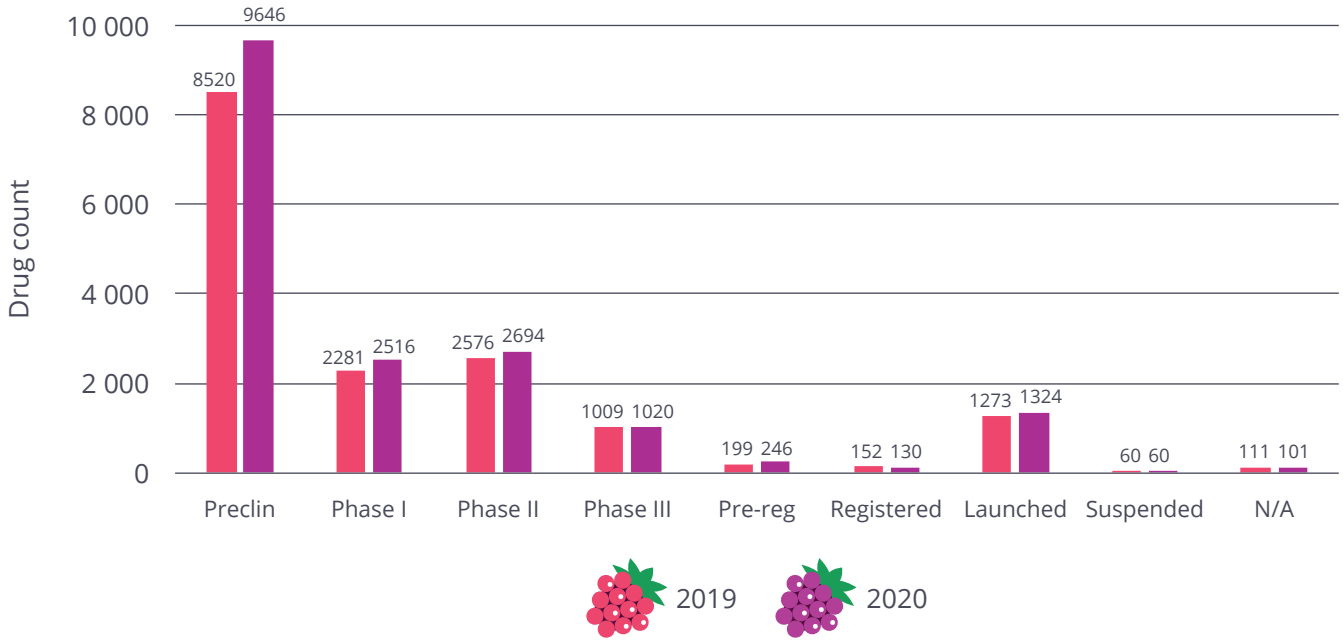
Well, this particular souped-up score comes with a side-order of caution. Just as with a good meal, more is not always better, and the bigger the volume of drugs in development, the more likely the industry is to suffer from a bad case of indigestion. Remember, the vast majority of these drugs are in pre-launch phases, so are costs, not earners. In recent years, the expanding waistline of the pipeline has at least been matched by increases in new drugs successfully making it onto the market. 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, which will follow. However, preliminary figures indicate that 2019 did not match the record-breaking 68 new drugs launched for the first time seen during 2018.

So, are the industry's eyes getting too big for its belly? Unless it can continue to provide the market with tasty new treats, then a certain degree of portion control in the pipeline might be advisable. You certainly *can* have too much of good thing: I was reminded with the recent sad death of former *Monty Python* team member Terry Jones of one of his most famous creations, Mr Creosote, a bon viveur who eats so much that he eventually explodes. Might pipeline expansion one day go the same way? Certainly R&D continues to be eye-wateringly expensive, and, as there's no such thing as a free lunch, costs must be kept under control, or the bubble will similarly collapse like an overcooked soufflé.

Hors D'oeuvre – The 2020 Pipeline by Phase
Will larger portions early in the meal sate pharma's hunger?

Figure 2 breaks that 17,737 number down by global development phase – the different 'courses' a drug development meal moves through. Reflecting that big rise in the number of new drugs identified during 2019, the volume of drugs at the preclinical stage posts an increase which is certainly no mere trifle – up by 1,126 drugs to 9,646, which is a striking 13.2% rise. There is also a big percentage increase in the number of drugs awaiting approval, perhaps in part a hangover of the US FDA's shutdown early in the year. But it is the clinical courses which as usual provide the most food for thought.

Figure 2: Pipeline by development phase, 2020 versus 2019



Note: N/A = Not Applicable and is applied to Companion diagnostics prelaunch.

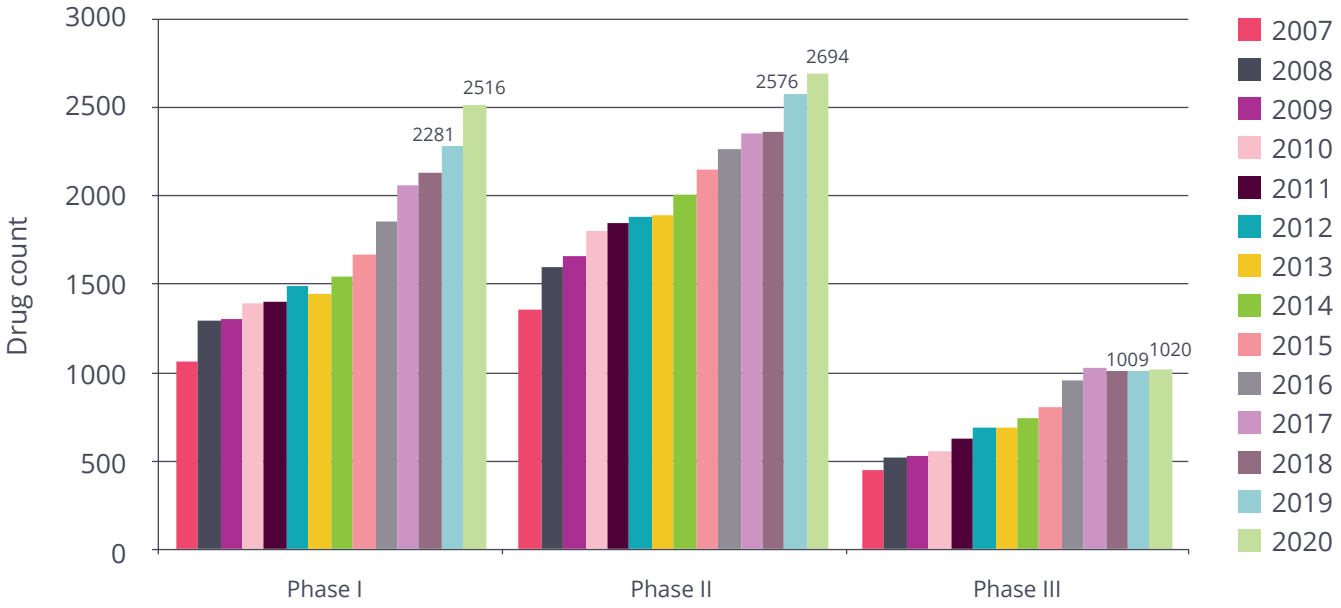
Source: Pharmaprojects®, January 2020

The increase in the number of drugs in Phase I clinical trials also outperformed the overall pipeline expansion figure, hitting 10.3%, beating the 7.2% seen last year and the 3.0% from the year before. However, the reverse is true for Phase II, where the increase of 4.4% was lower than 2019's 9.2%. But once again, neither of these two rises flow through to Phase III, which is only up by 1.9%. So, there is still considerable failure at Phase II, where there is arguably the biggest productivity challenge. Focusing on programmes with a higher likelihood of progressing (due to

factors such as better biomarkers or genetically defined subpopulations) could be a way of overcoming this barrier. After all, the industry can only sustain a certain amount of R&D spend, and Phase III is where most of this goes. Better to have the finest quality ingredients for the most expensive course, otherwise, the grocery bill really will get out of control.

This trend is again emphasized if we look further back through the years at the numbers of drugs in each clinical stage (Figure 3). Although we have seen year upon year of increases at Phases I and II, Phase III has stayed resolutely flat for the past four years. Too many drugs are still having to leave the table feeling a little queasy after Phase II.

Figure 3: Clinical phase trends, 2007–2020



Source: Pharmaprojects®, January 2020

In total, in 40 years of Pharmaprojects, we have now reported over 80,000 drugs, with the 17,737 Active drugs (which are the focus of this report) being augmented by over 4,200 Widely-Launched drugs, and a huge 58,000+ Ceased drugs – those which have been discontinued, withdrawn, or whose development lapsed. That's an awful lot of leftover food being thrown out in the garbage bins. Gordon Ramsay, the TV chef famed for yelling expletives at failing restauranteurs, would indeed have a nightmare. And maybe, pharma is a little too keen to throw away the leftovers. Through 2019, 3,399 drugs were moved to a 'Ceased' status – 91 more than in the previous year. But in pharma, the food-based adage that you can't make an omelette without breaking eggs has always been particularly apposite.

Main Course – Top Companies
Pharma's gourmands grow leaner, but are they fitter?

Let's move on to see who the industry's biggest movers and shakers are – the pharma companies with most on the menu. The big cheeses in our Top 25 list of companies by pipeline size for 2020 are listed in Table 1. All of these companies are of course huge multinationals, so their equivalents in the restaurant trade would be the biggest companies by market cap in this area. However, since these are headed by McDonald's, Starbucks and Yum! Brands (owners of KFC, Pizza Hut and Taco Bell), all fast-food joints, the big pharmas might not like to compare themselves to this industry here, since I'm sure they prefer to see their products more along the lines of vintage wines rather than burgers. In truth of course, many of the most successful pharma companies have a well-balanced portfolio, producing everything from cheap as chips generics to high-end niche cordon bleu orphan drugs for rare diseases.

Cream of the crop for a fourth consecutive year is Novartis, which increases its pipeline size only slightly, but has extended its lead over its nearest rival, Takeda. The Swiss conglomerate also has by some distance the most self-originated drugs, at 139. Unlike 2018, last year was a productive year for the company, and it brought home the bacon with no fewer than five NAS launches, across five different therapeutic areas. For breast cancer, it launched Piqray (alpelisib); for wet age-related macular degeneration it delivered the monoclonal antibody Beovu (brolucizumab); in multiple sclerosis it served up Mayzent (siponimod); for sickle cell anaemia it cooked up Adakveo (crizanlizumab); and, via its acquisition of AveXis, there was the spinal muscular atrophy gene therapy Zolgensma (onasemnogene abeparvovec). So, a year to dine out on its successes for the firm, which should maintain its position at the head of the top table.

In the runner-up position, Takeda's pipeline shrinks slightly as it continues with its digestion of Shire. The company leapt to number two last year following the acquisition, but its overall pipeline size may contract further as it continues to consolidate and remove further excess calories from its R&D diet. It's still highly notable to see a Japanese pharma company hit the heady heights, however. Bulking up this year though is Bristol-Myers Squibb, back into the top 10 after swallowing up Celgene. This was the third biggest pharma deal in history, eventually outstripping the Takeda/Shire tie up. Will this deal have the right ingredients to serve up a tasty concoction? Certainly, it bolsters BMS's oncology franchise significantly, and Celgene shareholders received a good price, but what it will mean for the Celgene R&D franchise is anyone's guess. History is littered with examples of takeovers where the larger company effectively stripped the meat from the bones of its acquiree to the extent that the smaller concern had effectively had its chips, if you'll excuse the mixed metaphor.

Table 1: Top 25 pharma companies by size of pipeline

Position 2020 (2019)	Company	No. of drugs in pipeline 2020 (2019)	No. of originated drugs 2020
1 (1)	Novartis	222 (219)	139
2 (2)	Takeda	198 (211)	89
3 (11)	Bristol-Myers Squibb	189 (110)	97
4 (3)	Johnson & Johnson	182 (208)	91
5 (6)	Roche	174 (189)	94
6 (9)	Pfizer	170 (163)	108
7 (4)	AstraZeneca	164 (194)	93
8 (8)	Merck & Co.	157 (176)	84
9 (7)	GlaxoSmithKline	144 (177)	77
10 (10)	Eli Lilly	143 (124)	85
11 (5)	Sanofi	137 (192)	62
12 (16)	Boehringer Ingelheim	108 (94)	73
13 (12)	Bayer	93 (108)	66
14 (13)	Otsuka Holdings	91 (98)	56
15 (19)	Amgen	89 (88)	59
16 (15)	AbbVie	89 (94)	31
17 (17)	Daiichi Sankyo	87 (92)	45
18 (20)	Eisai	84 (85)	48
19 (18)	Allergan	80 (90)	33
20 (21)	Astellas Pharma	75 (84)	39
21 (-)	Lee's Pharmaceutical	74 (-)	45
22 (23)	Gilead Sciences	73 (69)	39
23 (-)	Yuhan	72 (-)	57
24 (24)	Evotec	70 (63)	35
25 (22)	Ligand Pharmaceuticals	66 (73)	34

Source: Pharmaprojects®, January 2020

Elsewhere in the top 10, acquisitions were rife, but of a somewhat blander flavour, focusing instead on catching smaller fry to gain access to specific drugs or technologies. Merck & Co led the way with acquisitions of three companies: Immune Design, Peloton Therapeutics, and Tilos Therapeutics, while Novartis bolstered its position by absorbing IFM Tre (it's also started 2020 as it means to go on by completing a significant acquisition, that of The Medicines Company). Pfizer's climb up the charts was assisted by two takeovers, that of Theracon and the more sizeable Array BioPharma, while Roche gobbled up Jecure Therapeutics (via its subsidiary Genentech), and eventually enjoyed Spark Therapeutics for dessert in the dying days of the year. The latter deal

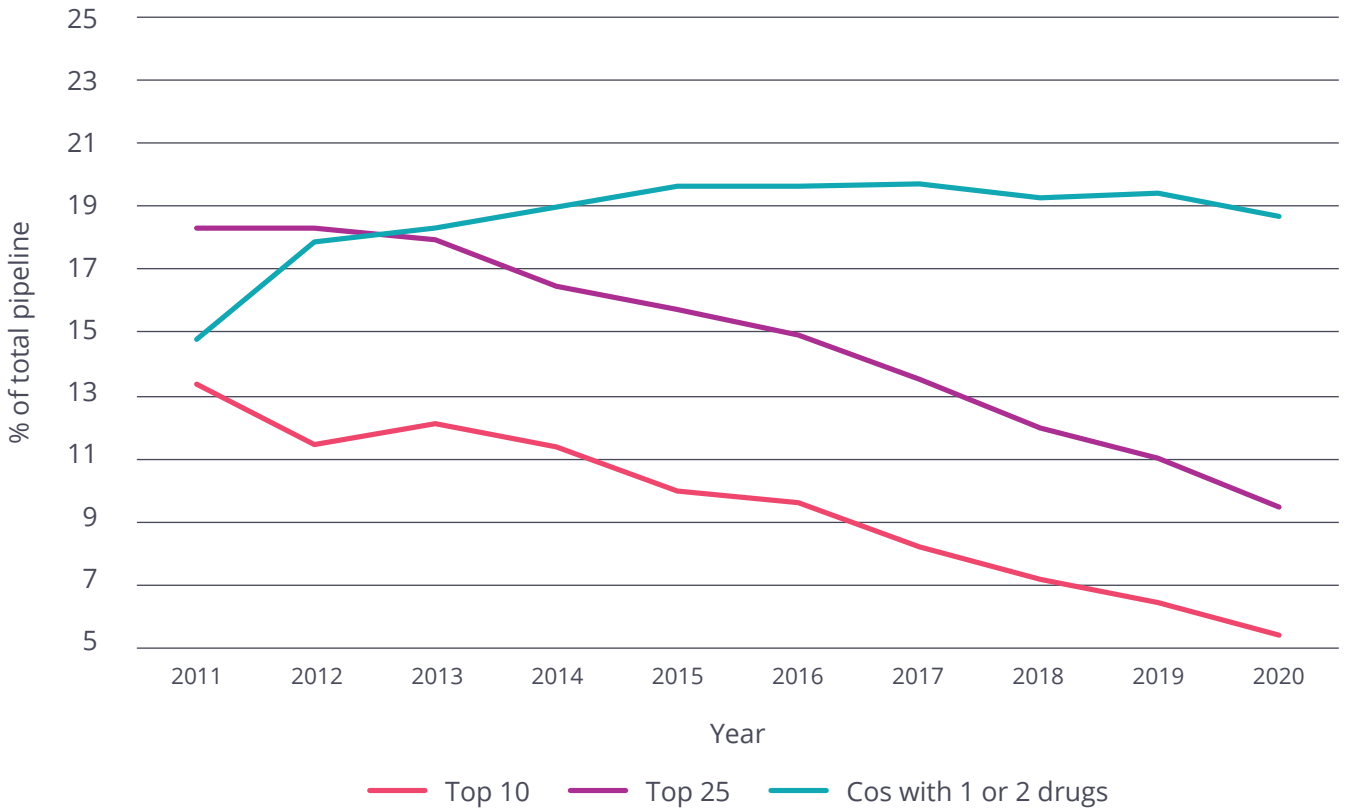
delivered the 2018 launch Luxturna (voretigene neparvovec) into Roche's clutches (although it is licensed-out to Novartis), along with a significant pipeline of similar gene therapies for rare diseases. GlaxoSmithKline also came to the party, despite posting a slimmed-down pipeline, buying both Tesaro and Sitari. Lilly retained its place in the lower reaches of the top 10 by eating up Loxo Oncology. Overall, deal-making of the M&A variety was at a similar level last year to that seen in 2018, with around 100 significant acquisitions reported. Will this continue in 2020? Many believe so: quoted in Informa's Insights publication Scrip[1], Jason Coloma, President of Maze Therapeutics, predicted that "Acquisitions will continue in a flurry, as IPOs and follow-on equity raises will become more difficult. The build-to-buy structure may start to be en vogue again," he noted.

The biggest decline in pipeline size came from French firm Sanofi, which this year fell out of the top 10 and posted a 29% slimming down of its pipeline. The company conducted a clear-out of its larder in February of last year, sending for recycling 38 products as it focused its menu more tightly on its core areas of oncology, immunology, rare diseases and rare blood disorders. There were two new entrants into the Top 25. Hong Kong-based Lee's Pharmaceutical becomes the first Chinese pharma company to enter the upper echelons of novel pharma R&D, while South Korean company Yuhan also entered two places below. But what's striking is that the majority of the companies in the table report smaller pipelines this year than last. Are those at the top table taking a smaller slice of the pie?

Well, the answer to that question is a resounding yes. Figure 4 examines how the share of the total pipeline which top companies contribute has been shifting over the past few years, and there's a definite continuation of the trend we've seen over recent years. In the graph, the pink 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. This has seen a further significant decline this year, to 5.40% (down from 6.45% in 2019). Similarly, the Top 25's contribution (purple line) is also heading further south, dramatically declining from 11.01% to 9.47% this year.

1. Scrip (2020) Scrip Asks... What Does 2020 Hold For Biopharma? Part 2: Business And Investment. Available from: https://scrip.pharmaintelligence.informa.com/SC141422/Scrip-Asks-What-Does-2020-Hold-For-Biopharma-Part-2-Business-And-Investment [Accessed 31 January 2020].

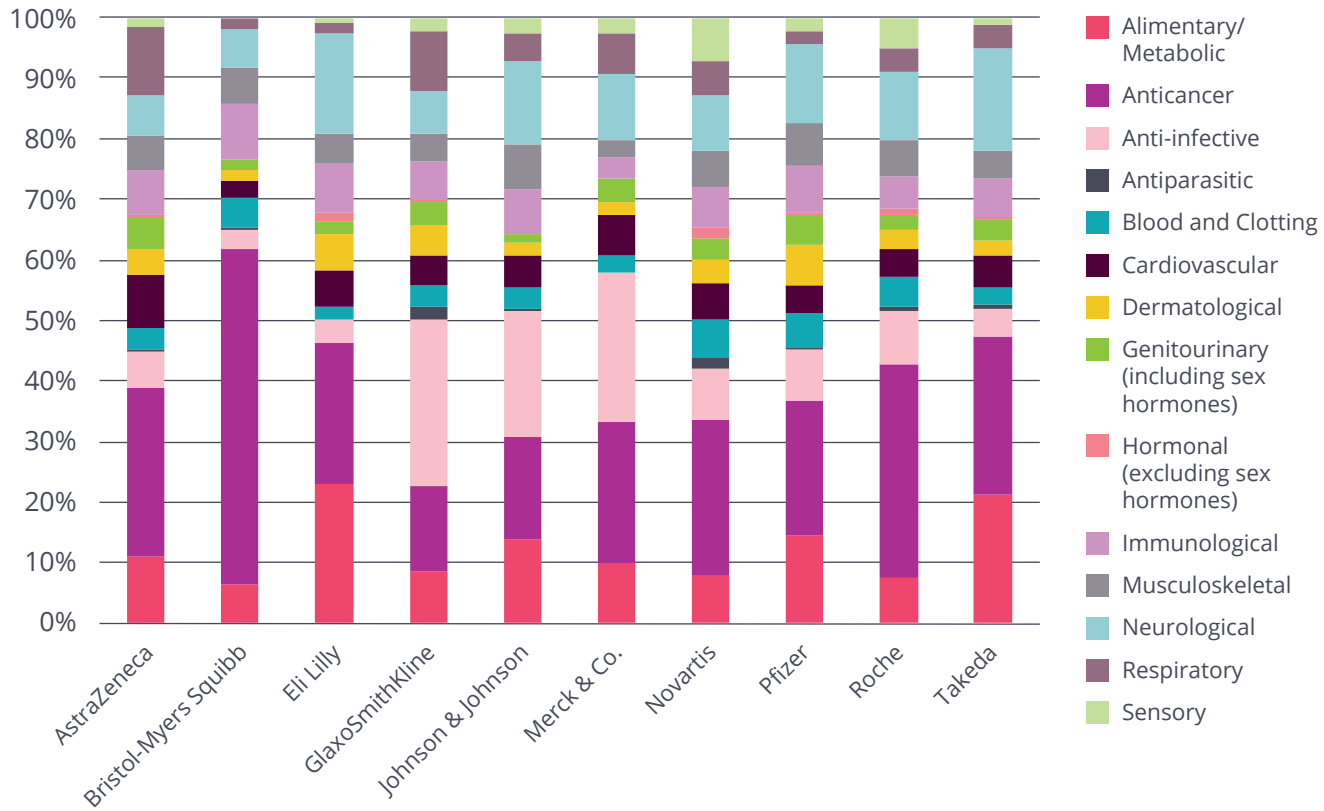
Figure 4: Share of the pipeline contributed by top 10 companies, top 25 companies, and companies with just one or two drugs



Source: Pharmaprojects®, January 2020

Is it the case that big pharma companies just don't cut the mustard anymore, or were they getting flabby and will benefit from being leaner and fitter? Part of the answer might be divined via an analysis which our new drug programme landscape enhancement permits us to undertake much more accurately. In Figure 5, you'll see, for each of the top 10 companies, the breakdown of their pipelines by therapeutic area.

Figure 5: Disease focus areas of the top 10 pharma companies



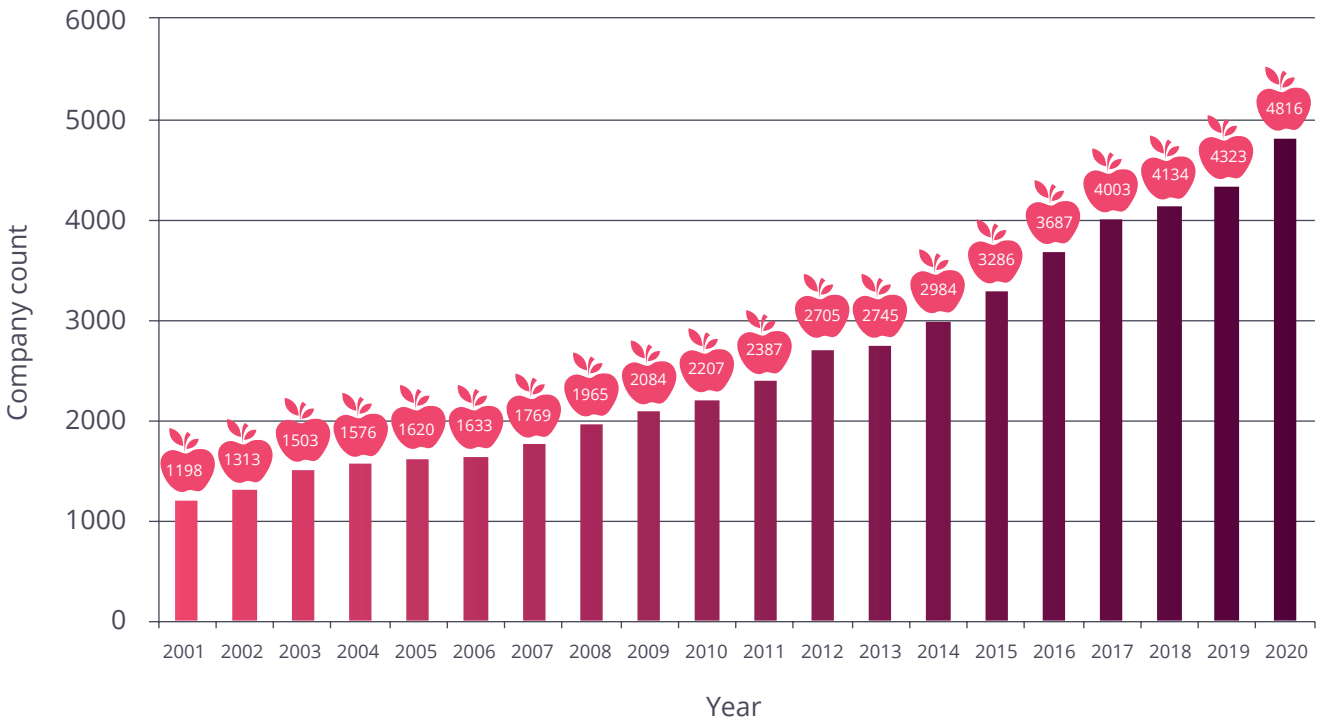
Source: Pharmaprojects®, January 2020

Perhaps what's most surprising here, in this era of companies producing pronouncements on how they're focusing on three of four key therapeutic areas, is the fact that the top 10 are still mixing up a heady cocktail of different kinds of drugs. Six of the 10 have at least one drug in all 14 therapeutic areas, and only two – Bristol-Myers Squibb and Merck & Co – have entirely exited more than one, although they are only absent from two minor areas, so are hardly an entirely different kettle of fish. One of these companies, BMS, exhibits the most intense single therapeutic focus, with over half of its drugs being in oncology. Yes, it's true that most are finding cancer, infection, alimentary/ metabolic, and neurological the juiciest areas, but it appears that diversity among the big fish remains intact. I must admit I was somewhat surprised by this outcome, as received wisdom dictates that companies are being egged on by their leaders to concentrate on a few core strengths, rather

than having fingers in every pie. So this will be a fascinating metric to follow over the coming years; one which will allow us to track whether companies really are rationalizing their menus to concentrate on a few specific cuisines.

Meanwhile, going back to Figure 4, we can see from the green line that pharma's small potatoes, the companies with just one or two drugs in their portfolios, continue to account for around 19% of the pipeline (there's a small but insignificant decline here). This is despite the fact that, unlike last year, the number of these companies, very much the bespoke family-run bistro as opposed to a Burger King, rose. As of January 2020, we report 735 companies with two drugs in their portfolios, up from 669 last year, and – this is a real whopper – 1,849 with a single drug; a huge increase from the 1,633 reported in 2019. That's 53.7% of all companies. It appears that there is a rich broth of smaller companies overall though, with 4,404 companies, or 91.4% of the total, with fewer than 10 drugs in their pipelines. These smaller companies account for 61.9% of the pipeline as a whole.

Figure 6: Total number of companies with active pipelines, 2001–2020



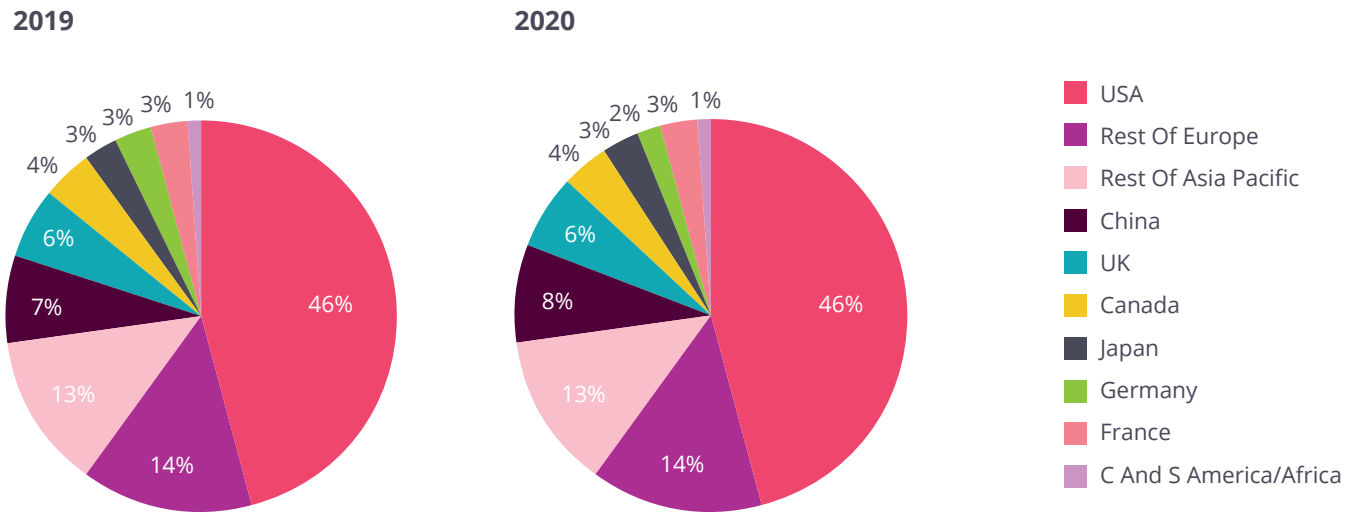
Source: Pharmaprojects®, January 2020

Blended together, the full range of ingredients of the stew of pharma companies amounts to 4,816 firms this year – an increase of 493 companies, or a gut-busting 11.4% (see Figure 6). That's both the biggest actual increase, and the biggest percentage increase, we've ever seen. The extra calories here are being fuelled massively by the largest number of new companies joining the

R&D repast reported in a single year. During 2019, we identified 809 new pharma and biotech companies as joining the pharma gravy train, beating the previous record of 750 from 2016, and 2018's 722. Thus, if 809 companies joined the pharma business during the year, but the total number only rose by 493, that means that 316 firms fell out of the R&D larder, due to merger, acquisition, failure, or hibernation. This is a lower number than the 533 lost during 2018, but this may be a reflection of variations in editorial practice more than genuine better company survival rates. Nevertheless, the high entry rate would seem to suggest a positive environment for start-ups.

Where is all this activity occurring? Not surprisingly, pharma R&D remains, like food consumption, firmly concentrated in the so-called developed world. In fact, it's interesting to compare how much food production and consumption, and pharma production and consumption, mirror each other. The US comes out top on food consumption, with a bunch of well-fed European countries following on. Meanwhile, Eritrea sits below a host of other African states, according to data from the Food and Agriculture Organization of the United Nations. As Figure 7 illustrates, this is not dissimilar to the distribution of drug companies across the globe.

Figure 7: Distribution of R&D companies by HQ country/region, 2019 and 2020



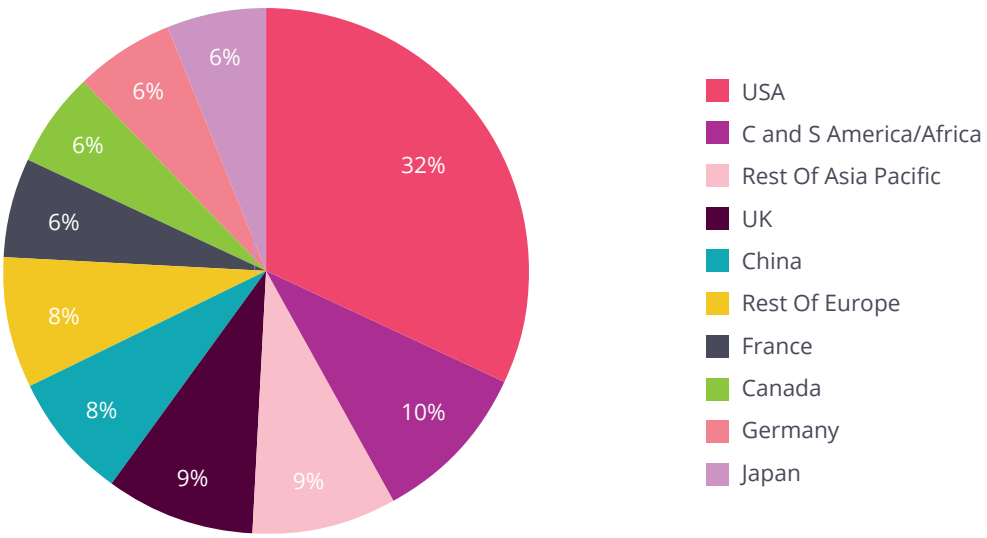
Source: Pharmaprojects®, January 2020

The lion's share of pharma company bases remains in the US, with this single territory playing maître d'hôtel to 46% of all drug developing companies, unchanged from last year's percentage. European concerns take up another quarter of all R&D, very slightly down on last year, with, perhaps surprisingly, Germany the territory to shrink a little (the dog's dinner of Brexit appears to have had little effect on the UK – yet). This appears to have come to the benefit of China, which is continuing in its bid to be as big a player in drug development as it is in food supply (I'm yet to visit a country

which doesn't boast at least one restaurant run by representatives of the Chinese diaspora). It's up a further percentage point share-wise, which doesn't sound super-significant, but actually represents a rise in the number of Chinese-headquartered companies developing novel drugs from 301 last year to 422 this – an expansion of 41%. This means that the Sinopharma advance is gaining pace, as the number of companies only grew by 15% last year. Contrast this with the whole of two continents – Africa and Central and South America – which provide just 1% of firms. Aside from the rise of China, pharma's power remains where it always has been.

However, thanks to our new drug programme landscape data enhancement, this year, we can dig a little deeper, and investigate not only where R&D companies are based, but where that R&D is genuinely taking place, with pinpoint accuracy not available before. As Figure 8 shows, this gives a much more even distribution, with just shy of a third of development occurring in the US. France has the second largest piece of the pie, with 10%, followed by China with 9%, and the UK with 9%, and the Rest of Europe (which excludes the UK, France, and Germany) on 8% each. So, while actual R&D still heavily leans US-ward, drug development is somewhat less concentrated there than the company headquarters are.

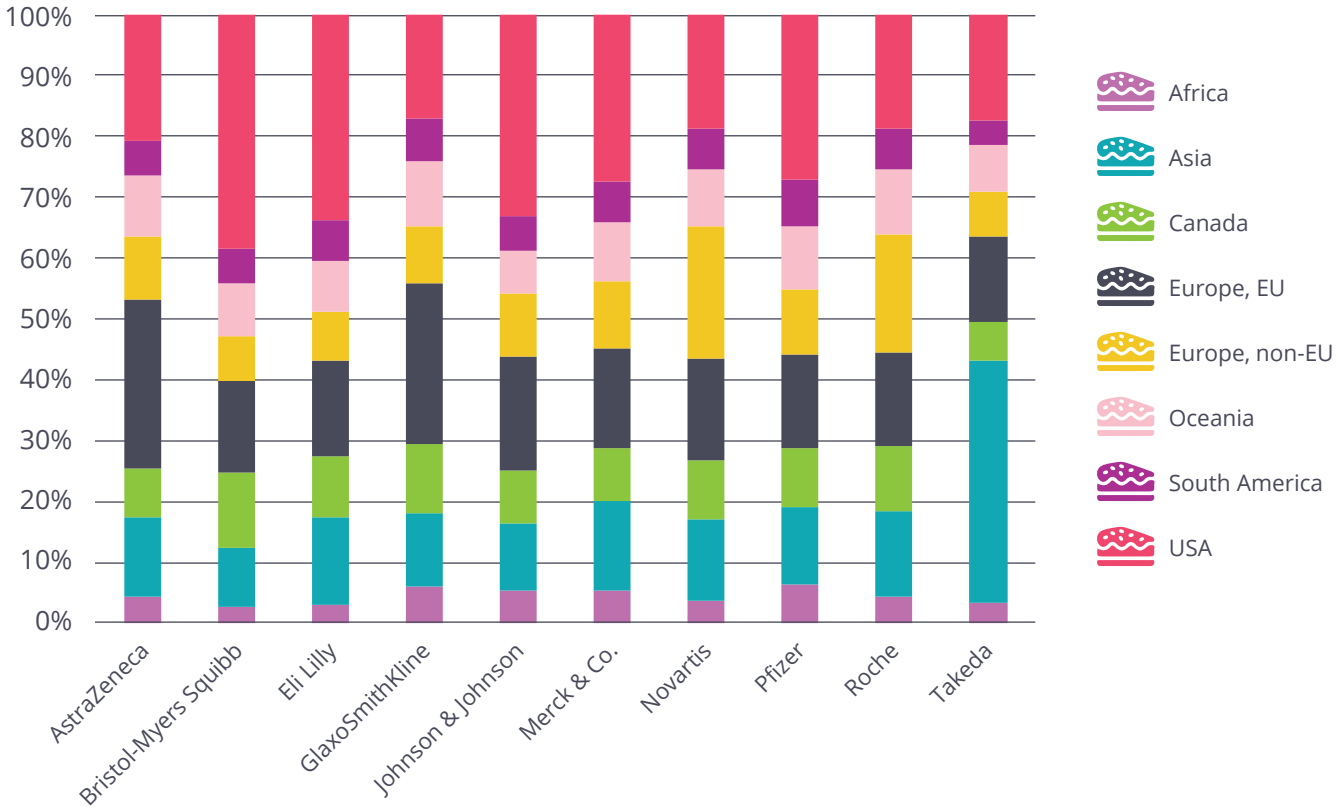
Figure 8: Where is R&D actually occurring?



Source: Pharmaprojects®, January 2020

We can also look at precisely where the biggest companies are developing their drugs by region, an analysis that also wasn't possible prior to 2020's enhanced data structure – see Figure 9. This breaks down the location of each of the top 10 pharma's R&D activities by the regions which our new data fields use (aside from North America being split out into Canada and USA for clarity). It therefore illustrates where each of these megacompanies is really performing its drug development.

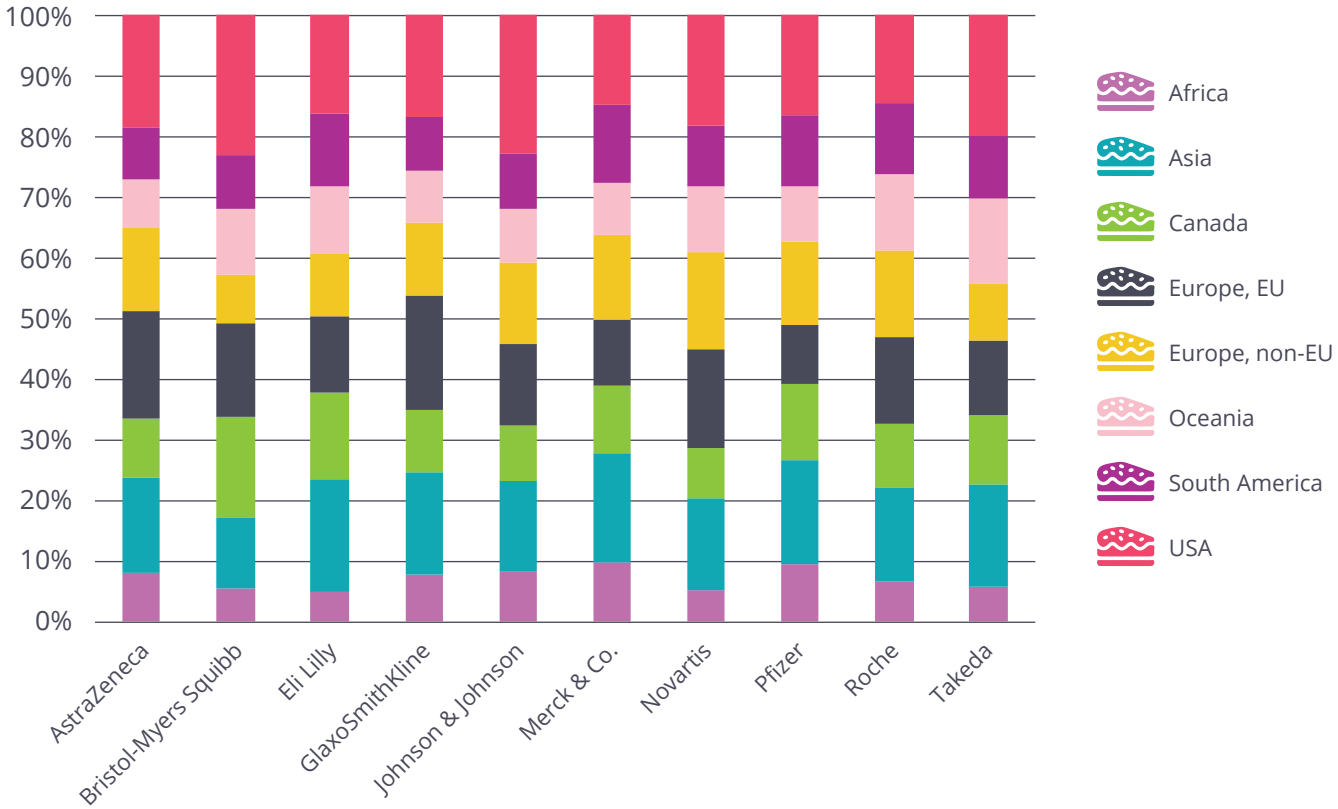
Figure 9: Where are the top 10 companies developing their drugs?



Source: Pharmaprojects®, January 2020

There are some fascinating – if not wholly unsurprising – variations in where the big multinationals choose to undertake their drug development. Three US firms – Eli Lilly, J&J, and Pfizer – are also the three with the largest proportion of pipeline development in the US, whereas UK-based AZ and GSK have the most EU-centric development (at the time of writing, the UK was still in the EU – just!). In contrast, and unlikely to raise many eyebrows, Takeda's R&D remains firmly ensconced in Japan. It's worth noting that these figures may somewhat be skewed towards companies' 'home' countries, as if we are unable to assign a territory to an early project, we assign it by default to the company's country of headquarters. So, let's repeat this analysis for drugs in Phase II and Phase III only, in an effort to remove this bias (see Figure 10).

Figure 10: Where are the top 10 companies developing their Phase II and Phase III drugs?



Source: Pharmaprojects®, January 2020

This changes the picture considerably, and very much evens things out. Takeda now has the third-largest activity percentage in the US, after Johnson & Johnson and Bristol-Myers Squibb. It clearly knows which side its bread is buttered. There are much more similar amounts of activity between companies across other major regions such as Asia, the EU, and the rest of Europe. There is still some discernible preference for companies to have their cookouts in their own backyards – the biggest EU bars are for AstraZeneca and GlaxoSmithKline. But what the graphic really illustrates is how all the big pharmas truly operate globally; all of them have significant Phase II and III development in every part of the world.

Second Course – Top Therapies
At the top table, the oncology feast continues

After a quick palette cleanser, it's time to move on to our secondi, as we examine the therapeutic areas and diseases where pharma development is focused. We'll start with the broad therapeutic areas – the cuisines of pharma – before moving on to the cooking styles of therapeutic categories, and then the individual dishes of disease development.

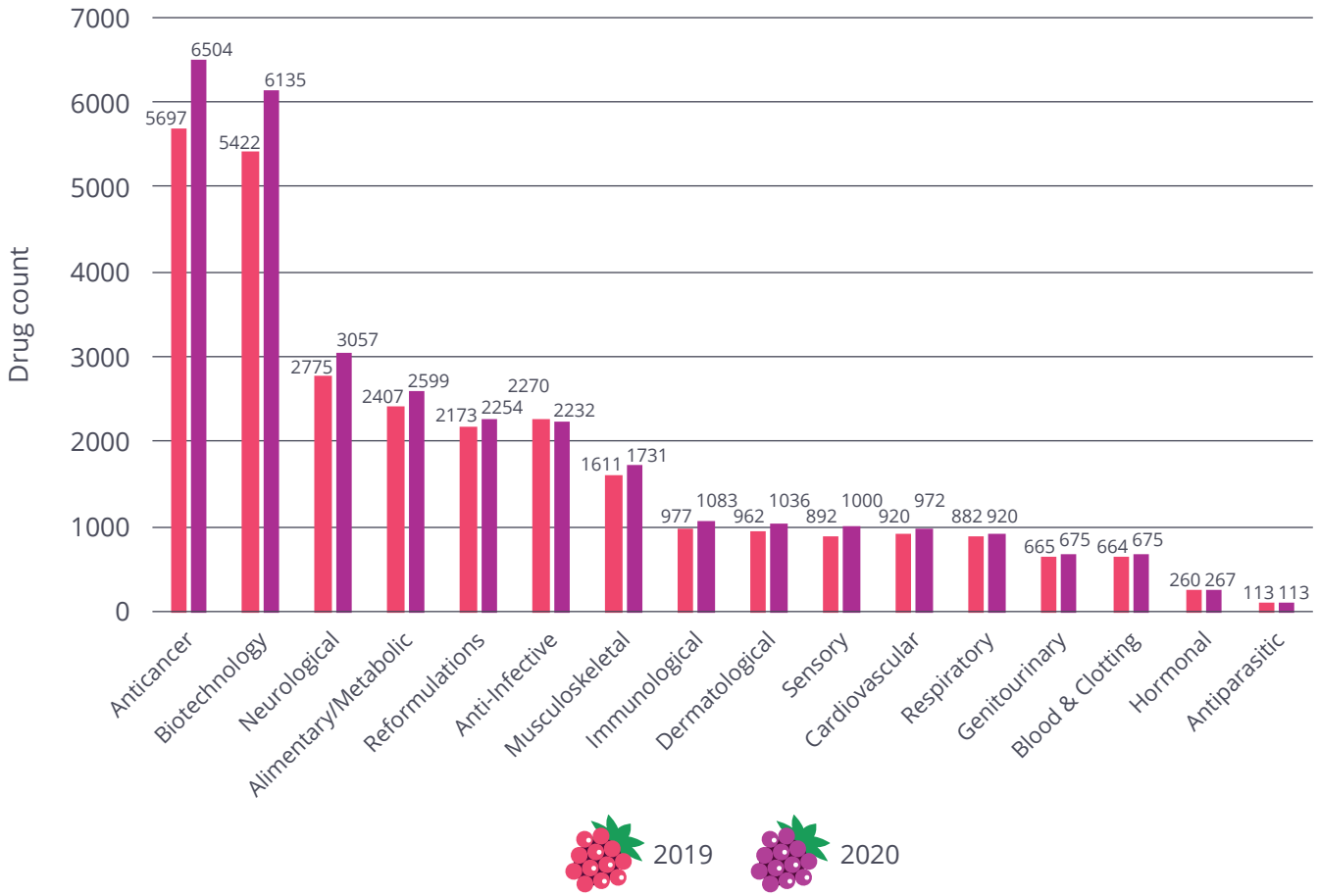
According to a YouGov survey of more than 25,000 people in 24 countries who were asked whether they had tried 34 different cuisines and whether or not they had liked them[2], Italian cuisine is the most popular in the world. Pizza and pasta are pre-eminent – even if they do have something of a link with drugs for obesity and cardiovascular disease! Chinese came second, with Japanese third. The survey found that UK food was viewed particularly disdainfully by mainland Europeans – proof that as in politics, so in food, perhaps! Something of a subjective survey for sure, and to be taken with a generous pinch of salt, but also, there's nothing counterintuitive here.

The most 'popular', if that's the right word, therapeutic area for drug development is once again cancer. The 2020 data shows the pre-eminent disease of our time increasing its stranglehold on therapeutic development further. With 6,504 drugs in R&D, cancer candidates comprise 36.7% of all of pharma's larder, and the total oncology franchise has grown by 14.2%, outpacing once again the overall level of pipeline expansion. This percentage growth rate was not the highest seen this year though, with Biotechnological drugs, not really a Therapeutic Area but included in this analysis nonetheless, increasing by 13.2%. It's worth noting that in this data, represented in Figure 11, there can be considerable double-counting, as drugs may be under development in more than one therapeutic area. This is particularly true in the case of oncology and biotechnology, which go together as often as pasta and sauce in the 2020 R&D landscape, thanks in no small part to the rise of immuno-oncology, of which more later.

Following on from these two behemoths of R&D, Neurologicals post fewer than half as many candidates, and show a more modest increase, with a 10.2% growth rate (still outpacing the overall 9.6% reported earlier), with Alimentary/Metabolics up by a smaller portion (8.0%). It's notable then – and extremely concerning – to see that Anti-infectives actually posted a decline this year, down 1.7%. In an environment where the overall pipeline growth rate is nearly 10%, to post such a shrinkage clearly represents a significant move away from this area. It was also the only therapeutic area to record an actual decline. And this is at a time where the growth of antimicrobial resistance means that the need for new antibacterial drugs is more pressing than ever, and a zoonotic viral infection is causing worldwide consternation.

2. YouGov (2019) Italian cuisine is world's most popular. Available from: https://yougov.co.uk/topics/food/articles-reports/2019/03/12/italian-cuisine-worlds-most-popular [Accessed 31 January 2020].

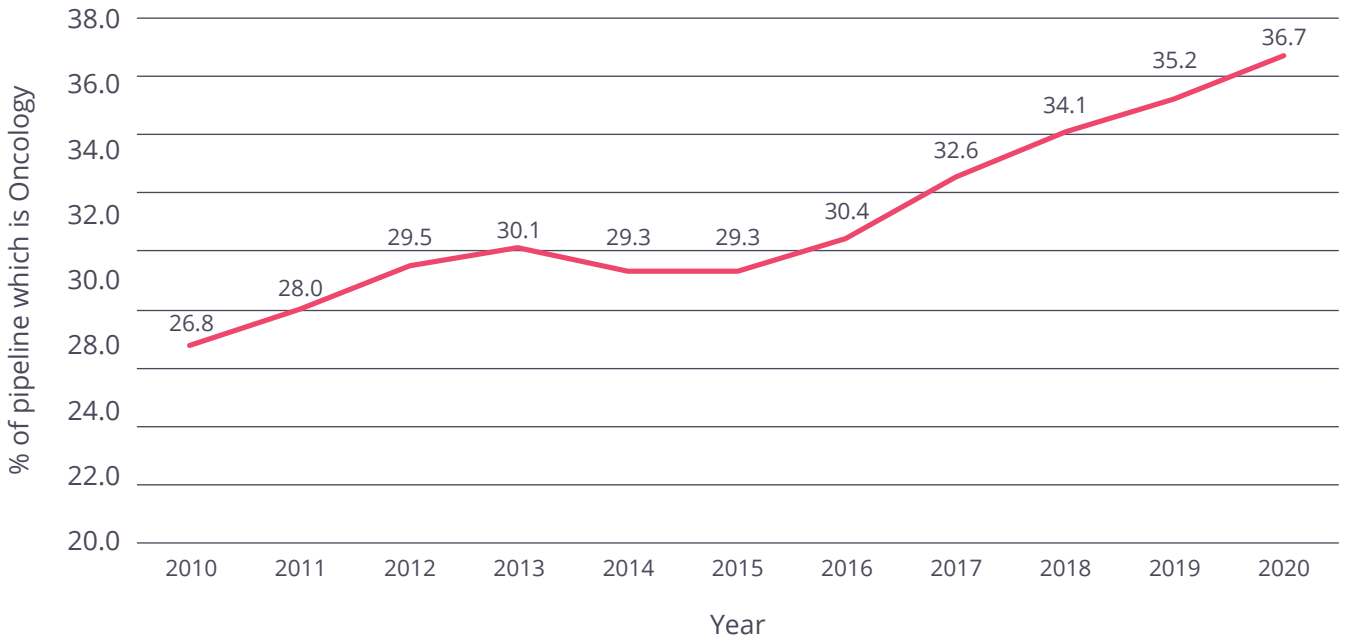
Figure 11: The R&D pipeline by therapy group, 2019 and 2020



Source: Pharmaprojects®, January 2020

Cancer's allotment has grown further this year, as it elbows its fellow diners out of the way to grab an ever-larger portion of the R&D cake. As Figure 12 shows, this upward trend has been continuing for pretty much all of the past decade. While there is still undoubtedly huge unmet need and drastic room for improvement in cancer therapy, there is a danger that the industry might put all its eggs in one basket. Having said that, advances in oncology are having genuine and measurable effects in producing declining mortality rates for many cancers. A recent NEJM article[3] clearly shows how death rates in Hodgkin's lymphoma, lung cancer, and chronic myelogenous leukaemia, among others, are coming down nicely, although the picture can be complicated in other cancers where improved screening or overdiagnosis affects incidence rates. The 2020s hold real promise that, as new immuno-oncological techniques reap further results, the mortality rates for this devastating disease will continue to decline.

Figure 12: Proportion of the pipeline which is in development for cancer, 2010–20



Source: Pharmaprojects®, January 2020

Table 2 breaks down these broad therapeutic areas into the more digestible 240 individual therapeutic categories. This year, with such a significant surge in the size of the overall pipeline, we've added to our Trend column an extra notation, ↑↑, to highlight those categories which aren't just expanding, but are expanding really rather a lot. This has been applied to

3. Welch HG, Kramer BS, Black WC (2019) Epidemiologic Signatures in Cancer. Available from: https://www.nejm.org/doi/full/10.1056/NEJMsr1905447 [Accessed 31 January 2020].

Anticancer, immunological, which holds firm for a second year at the summit, ahead of that old chestnut Anticancer, other (the general anticancer category). It's another big uptick for the leader, with just over a quarter as many again drugs as it had 12 months ago. The biggest increase is posted by the Cellular therapy, chimaeric antigen receptor, or CAR-T, category. This whisks into the Top 25 stiffened by a 77.9% boost in its pipeline size – quite remarkable for a technique which, thus far, has delivered all of two drugs successfully to the market: Kite/Gilead's Yescarta (axicabtagene ciloleucel) for lymphomas, and Novartis/Lentigen's Kymriah (tisagenlecleucel) for lymphomas and leukaemias. With only one further novel CAR-T therapy filed as yet, this is an approach which has barely been weaned onto solid food yet, but nonetheless holds out huge promise. [It's worth noting here that, as in Figure 13, drugs can appear in more than one category, so some of the uptick in CAR-T and anticancer immunologicals will have been brought about by the same drugs].

Table 2: Top 25 therapeutic categories

Position 2020 (2019)	Therapy	No. of R&D products 2020 (2019)	Trend
1 (1)	Anticancer, immunological	3,434 (2731)	↑↑
2 (2)	Anticancer, other	2,510 (2450)	↔
3 (3)	Gene therapy	1,273 (864)	↑↑
4 (4)	Monoclonal antibody, other	1,009 (818)	↑↑
5 (6)	Ophthalmological, other	756 (690)	↑
6 (5)	Prophylactic vaccine, anti-infective	698 (702)	↔
7 (8)	Neurological	666 (567)	↑
8 (7)	Antidiabetic	589 (571)	↔
9 (9)	Immunosuppressant	544 (511)	↔
10 (10)	Anti-inflammatory	529 (473)	↑
11 (15)	Monoclonal antibody, humanized	508 (455)	↑
12 (11)	Musculoskeletal	504 (461)	↔
13 (20)	Reformulation, other	492 (408)	↑
14 (33)	Cellular therapy, chimaeric antigen receptor	491 (276)	↑↑
15 (14)	GI inflammatory/bowel disorders	488 (459)	↔
16 (19)	Cardiovascular	468 (412)	↑
17 (13)	Cognition enhancer	466 (459)	↔
18 (12)	Monoclonal antibody, human	448 (461)	↓
19 (21)	Analgesic, other	448 (390)	↑
20 (18)	Biosimilar	442 (432)	↔
21 (24	Neuroprotective	421 (386)	↑
22 (16)	Reformulation, fixed-dose combinations	419 (446)	↓
23 (29)	Hepatoprotective	418 (340)	↑↑
24 (30)	Dermatological	408 (339)	↑↑
25 (22)	Metabolic and enzyme disorders	400 (389)	↔

Source: Pharmaprojects®, January 2020

Other high climbers include two of the categories covering monoclonal antibodies: the general Dermatological class, and Hepatoprotectives, the latter buoyed by the increasing focus on non-alcoholic steatohepatitis (NASH) now that hepatitis C is seen to be past its sell-by date. Conversely, the fashion for Biosimilars, the microwave ready meals of drug R&D, shows signs of peaking. But really taking the biscuit is Gene therapy. Although I highlighted its extraordinary comeback last year, I think this bears repeating this year, especially, as shown, the bounce back is continuing, fuelled in part by further CAR-T development (which is also classified as gene therapy). On Figure 13, the pink bars show the Gene therapy pipeline size going back as far as 1995, measured via the left-hand-side axis, whereas the purple line tracks its position in the therapeutic category league table according to the right-hand-side axis.

Figure 13: The ongoing rise of gene therapy

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

Source: Pharmaprojects®, January 2020

The graph shows that not everything heads skyward all of the time – the vagaries of scientific endeavour can sometimes lead to strategies going in and out of fashion, almost as dramatically as certain foods become the subject of fads. In the UK, there's a famous example of the latter, when in 1995, popular TV chef Delia Smith included cranberries in a non-Christmas recipe for duck, and sales jumped by 200% overnight. Nowadays, the trend is for 'superfoods', such as brassicas like kale, and the aforementioned quinoa, despite the fact that nutritionally speaking, the term superfood has no meaning. Thankfully, pharma trends are influenced less by smart marketing, and more by cold hard science. The Gene therapy story, as documented in last year's report, saw the strategy fall on hard times following clinical failures, only to be resurrected spectacularly and

ride on the coattails of the CRISPR and CAR-T revolution. We note that this year, this shows no sign of abating, with Gene therapies reporting a further 47.3% expansion. In R&D terms, the strategy is selling like hot cakes.

Delving into the therapeutic ingredients making up the pipeline even further, we move to individual diseases or indications. Here, the aroma of cancer's dominance becomes ever more pungent. Individual types of cancer moved to take control of the entire top five of the chart listed in Table 3 last year; this year they take the top seven. Breast cancer lengthens its lead as the biggest crop, with a 19.4% rise in the number of drug candidates, but non-small cell lung cancer in second is also showing strong growth. Pancreatic moves up a place at the expense of ovarian, despite the latter also expanding its pipeline.

Table 3: Top 25 diseases/indications

Position 2020 (2019)	Disease*	No. of active compounds 2020 (2019)	Trend
1 (1)	Cancer, breast	924 (774)	↑↑
2 (2)	Cancer, lung, non-small cell	710 (586)	↑↑
3 (3)	Cancer, colorectal	640 (535)	↑
4 (5)	Cancer, pancreatic	563 (438)	↑↑
5 (4)	Cancer, ovarian	519 (442)	↑
6 (8)	Cancer, prostate	486 (366)	↑↑
7 (9)	Cancer, brain	479 (360)	↑↑
8 (6)	Alzheimer's disease	459 (405)	↑
9 (12)	Arthritis, rheumatoid	454 (335)	↑↑
10 (10)	Cancer, melanoma	440 (357)	↑
11 (7)	Diabetes, Type 2	434 (382)	↔
12 (11)	Cancer, leukaemia, acute myelogenous	404 (338)	↑
13 (13)	Cancer, myeloma	393 (283)	↑↑
14 (16)	Cancer, liver	357 (273)	↑
15 (15)	Cancer, gastrointestinal, stomach	354 (276)	↑
16 (14)	Cancer, head and neck	354 (283)	↑
17 (17)	Parkinson's disease	345 (271)	↑
18 (19)	Psoriasis	330 (260)	↑
19 (18)	Pain, nociceptive, general	319 (266)	↔
20 (20)	Cancer, lymphoma, non-Hodgkin's	315 (231)	↑↑
21 (21)	Non-alcoholic steatohepatitis	309 (222)	↑↑
22 (22)	Cancer, renal	277 (221)	↑
23 (23)	Asthma	255 (196)	↑
24 (26)	Pain, neuropathic, general	244 (178)	↑
25 (28)	Crohn's disease	236 (167)	↑↑

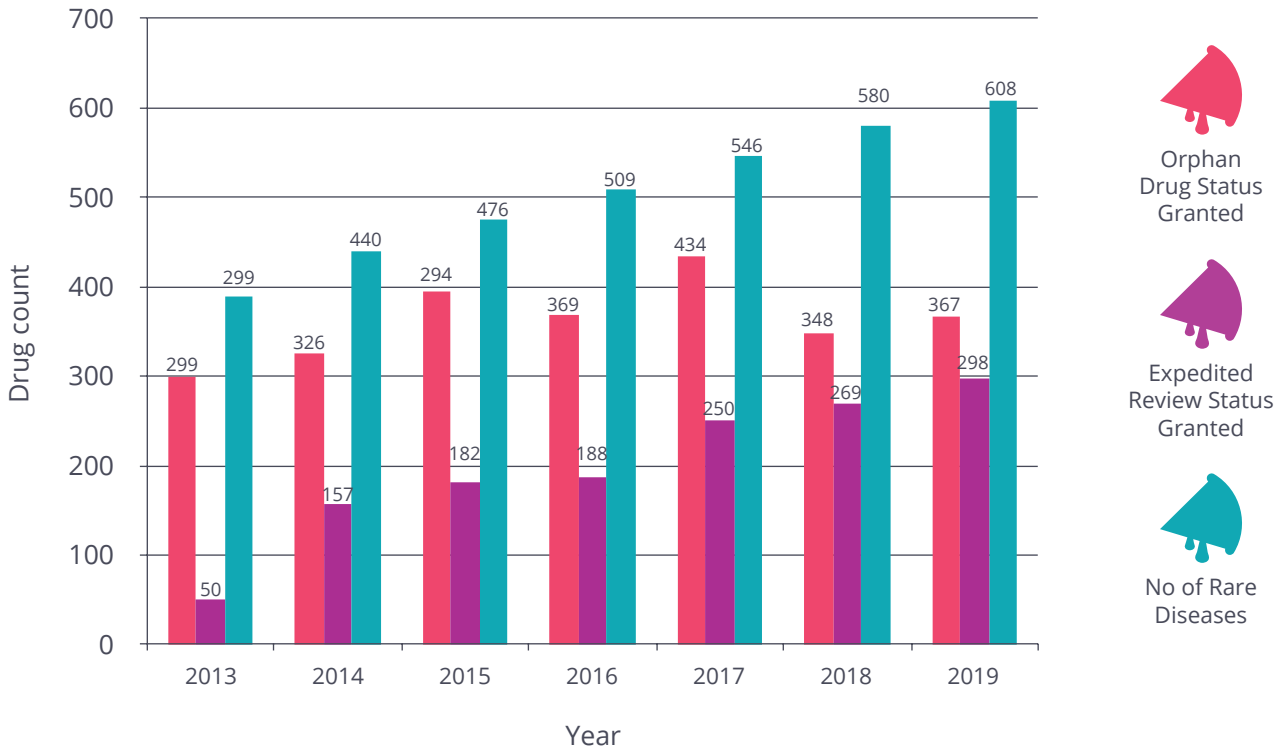
**Excludes the more generalized indications which include the term 'unspecified' to focus in solely on counting drugs where precise target diseases have been identified.*

Source: Pharmaprojects®, January 2020

But it's prostate and brain cancer which make the most notable advances, cementing cancer's hold on the top seven at the expense of type 2 diabetes and Alzheimer's disease, which remains a tough nut to crack. Once again, the year saw high-profile AD trials go pear-shaped, and late-stage drugs get in a pickle. Biogen and Eisai's anti-amyloid antibody aducanumab failed in Phase III in March, but by October, it was the recipient of a more positive spin and a tentative resuscitation. The companies might want to take a glance over at Roche's crenezumab which, after a similar stay of execution a few years back, is persisting in new Phase II studies for now, but ultimately still might not escape the slaughterhouse. However, the conundrum of Alzheimer's is still the biggest focus for R&D outside of cancer. Cancer now takes 14 of the top 20 slots, with particularly big increases for myeloma, liver, and NHL.

Drugs for rare diseases, like rare foods, can command high prices. Saffron is reckoned to be the world's most expensive foodstuff by weight, based largely on the painstaking harvest process it takes to produce this highly prized spice. A single pound can cost $5,000. Other rare and therefore costly delicacies include Almas caviar, black truffles, Densuke watermelon, and if you have the stomach for it and are presumably Icelandic, raw puffin heart. For a number of years now, rare, often genetic diseases have been a focus for an industry seeking to serve up to patients unique and premium-priced therapies, and 2020 is no exception. The number of drugs in development for rare diseases has now reached 5,287 – almost one in three. This is up from 4,953 last year. [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)]. As Figure 14 shows, therapeutics are under development now for 608 individual rare diseases. Concomitantly, the number of orphan drug and expedited review designations granted has also risen (both are associated with rare disease development).

Figure 14: Rise in numbers of drugs receiving Orphan Drug status or an Expedited Review designation*, and the number of rare diseases under investigation, 2013–19



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

Source: Pharmaprojects®, January 2020

Once again, we can delve a little deeper this year thanks to our enhanced drug programme landscape data, so I thought it would be interesting to see if there are regional variations in which diseases are being targeted the most. And indeed, the variations are as considerable as the differences in each region's cuisine. Table 4 shows the top eight indications by numbers of drugs in development for each region.

Table 4: Regional variations in R&D, by disease

Position/ Region	Africa	Asia	Canada	EU	Europe, non-EU	Oceania	South America	US
1	Diabetes, type 2	Cancer, breast	Cancer, breast	Cancer, breast	Cancer, breast	Cancer, breast	Cancer, breast	Cancer, breast
2	Cancer, breast	Cancer, lung, non-small cell	Cancer, lung, non-small cell	Cancer, lung, non-small cell	Cancer, lung, non-small cell	Cancer, lung, non-small cell	Arthritis, rheumatoid	Cancer, lung, non-small cell
3	Infection, HIV/AIDS	Cancer, colorectal	Cancer, colorectal	Arthritis, rheumatoid	Arthritis, rheumatoid	Cancer, melanoma	Cancer, lung, non-small cell	Cancer, pancreatic
4	Arthritis, rheumatoid	Cancer, gastrointestinal, stomach	Cancer, leukaemia, acute myelogenous	Cancer, ovarian	Diabetes, type 2	Diabetes, type 2	Diabetes, type 2	Cancer, ovarian
5	Chronic obstructive pulmonary disease	Diabetes, type 2	Cancer, ovarian	Diabetes, type 2	Crohn's disease	Cancer, leukaemia, acute myelogenous	Cancer, prostate	Cancer, leukaemia, acute myelogenous
6	Asthma	Cancer, liver	Cancer, myeloma	Cancer, leukaemia, acute myelogenous	Cancer, ovarian	Cancer, myeloma	Cancer, gastrointestinal, stomach	Cancer, myeloma
7	Haemophilia A	Cancer, pancreatic	Cancer, renal	Cancer, myeloma	Cancer, gastrointestinal, stomach	Cancer, pancreatic	Asthma	Cancer, liver
8	Infection, tuberculosis	Cancer, renal	Cancer, gastrointestinal, stomach	Cancer, gastrointestinal, stomach	Cancer, renal	Cancer, renal	Chronic obstructive pulmonary disease	Cancer, gastrointestinal, stomach

Key:

Cancer | Alimentary/Metabolic | Musculoskeletal | Respiratory | Infectious Disease | Blood & Clotting

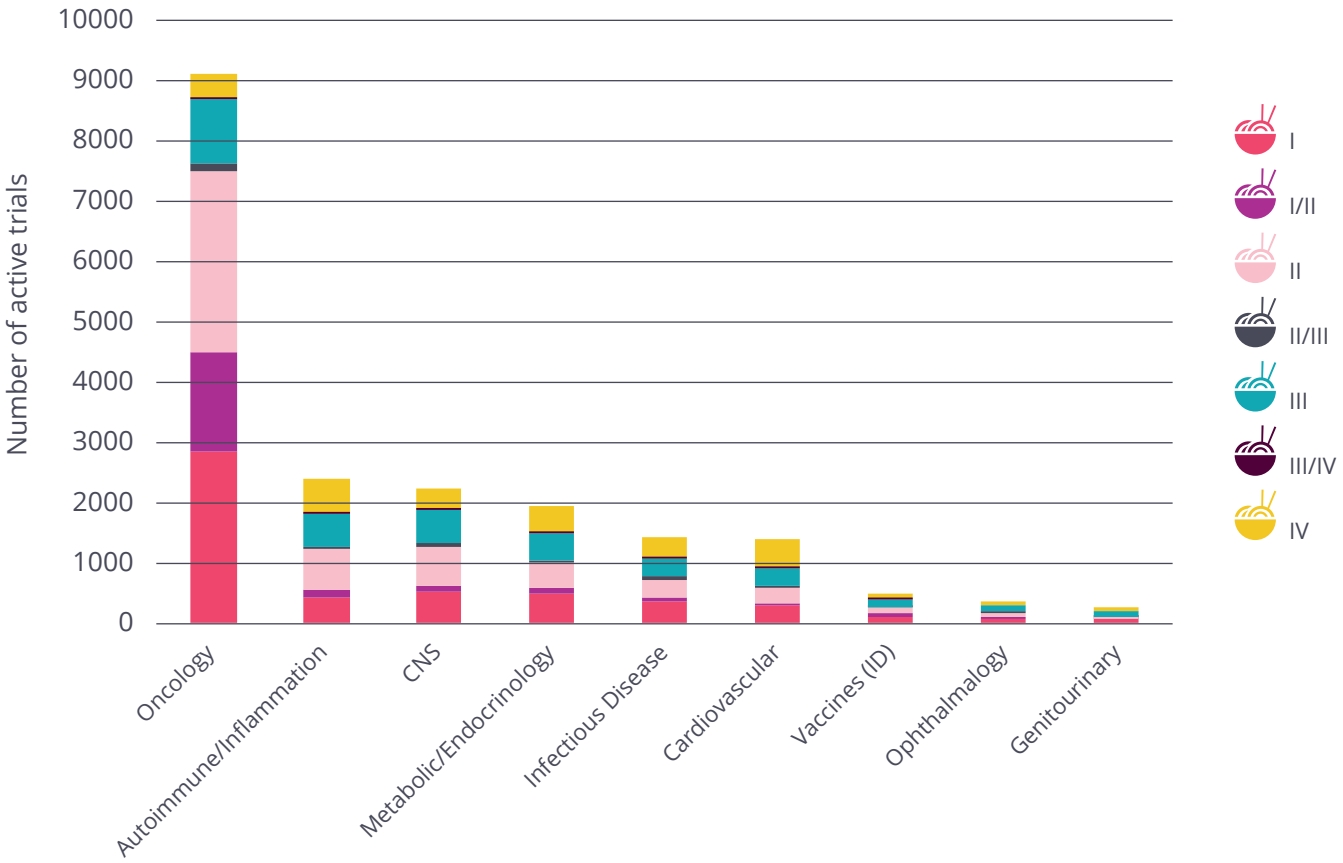
Source: Pharmaprojects®, January 2020

The data shows that, while breast cancer is pre-eminent in seven out of the eight regions, type 2 diabetes is the biggest focus of Africa-based R&D. This continent also serves up a number of other differences, with HIV/AIDS at number three, COPD at five, haemophilia A at seven, and tuberculosis at number eight, all reflecting its particular regional concerns. South America also bucks the trend of having breast cancer and NSCLC at one and two, with its runner-up being rheumatoid arthritis. Despite type 2 diabetes being in the top five for six of the regions, it's completely absent from the top eight for Canada and the US. These two countries both have a top eight entirely composed of different cancer indications. This new analysis provides a fascinating peek into the

drug kitchens of each region to see what is being cooked up where, and is a topic which I'm sure we'll return to in future years.

All our data thus far has been looking at numbers of drugs in development, but there is another way to assess R&D activity – by looking at numbers of individual clinical trials. Pharmaprojects is fully integrated with another Citeline solution, Trialtrove, which contains details of over 325,000 trial protocols and results. In Figure 15, we've compiled totals for the number of Active (Open, Closed or Temporarily Closed) trials by the therapeutic areas which are used in the Trialtrove database, broken down by trial phase.

Figure 15: Clinical trial landscape, by therapeutic area



Source: Trialtrove®, January 2020

This shows an even more marked concentration in Oncology. With over 9,000 active trials, this therapeutic area has almost four times as many trials underway currently as any other therapeutic area, and 46.4% of all trials. Why so? Well, cancer drugs are, particularly in the Phase I and II stages, often trialled for use in multiple different cancers; hence; they have a higher trial to drug ratio. But it's still a strikingly stark picture of just how far cancer has become very much the staple food of pharmaceutical R&D.

Third Course – Mechanisms and Targets
New recipes and novel ingredients adding spice to R&D

The human gustatory perception system – or taste – is still not entirely understood. The taste buds, of which we generally have around 2,000–5,000, each containing 50–100 taste receptor cells, have been shown to be able to detect distinctly the four basic tastes: sweet, sour, salt, and bitter, plus the more recently discovered savoury (often known as umami). But matters may be more complex than that, as various other 'basic' tastes have been proposed, such as spiciness, coolness (as in minty flavours), numbness, astringency, metallicness, calcium, fat taste, heartiness, and starchiness. Added to this, we can sense the temperature of our food and its texture via oral thermoreceptors and mechanoreceptors, respectively. But it's only when these basic building blocks are further combined with the more sophisticated olfactory system, which can detect hundreds of different smells, do we get the full and rich sense of flavour.

Similarly, the 80,000+ drug candidates on the Pharmaprojects database have been developed based on different combinations of a relatively small number of mechanisms of action and drug targets. The Top 25 mechanisms are shown in Table 5. The listing is, as ever, dominated by broader categories; our mechanism classification is hierarchical, and includes terms added to tag certain types of drugs. This has the effect of concentrating the drugs at the higher end of the hierarchy under broad terms, particularly for drugs in the earlier stages of development, where the precise nature of the drug's mechanism may be yet to be determined. Thus, all of the top eight in our table are rather general terms.

Spending its second year at the top after ascending last year is the Immuno-oncology category – very much the 'umami' of broader categories, having been only recently introduced in 2015. It is applied to all anticancer strategies where the therapy mobilizes the body's own immune system to identify and to attack its cancer cells, as opposed to drugs which act directly against a tumour. This year, it gains in weight a further 730 drug candidates, a rise of another 38.9%. This is even though, as the right-hand column shows, only 1.8% of the 2,605 drugs have reached the pre-registration, registered, or launched stages of development. In fact, there are still only 33 drugs on the market which use this strategy. The industry continues to show enormous faith in this approach, considering its relative newness.

Table 5: Top 25 mechanisms of action (pharmacologies)

Position 2020 (2019)	Mechanism of action (pharmacology)	No. of active compounds 2020 (2019)	% of compounds PR/R/L
1 (1)	Immuno-oncology therapy	2,605 (1,875)	1.8
2 (2)	Immunostimulant	1,293 (1,387)	12.5
3 (3)	T cell stimulant	718 (404)	1.3
4 (4)	Immune checkpoint inhibitor	404 (327)	3.2
5 (5)	Immunosuppressant	191 (199)	33.0
6 (6)	Angiogenesis inhibitor	191 (186)	19.4
7 (7)	Gene expression inhibitor	154 (154)	1.9
8 (9)	Radiopharmaceutical	147 (122)	6.1
9 (7)	Vascular endothelial growth factor (VEGF) receptor antagonist	140 (149)	14.3
10 (10)	Apoptosis stimulant	127 (127)	13.4
11 (-)	Genome editing	117 (-)	0.0
12 10)	Opioid mu receptor agonist	114 (116)	34.2
13 (14)	Immune checkpoint stimulant	113 (99)	0.0
14 (21)	PD-L1 antagonist	103 (74)	2.9
15 (130)	CD3 agonist	100 (22)	1.0
16 (13)	Cyclooxygenase 2 inhibitor	100 (103)	32.0
17 (18)	PD-1 antagonist	99 (83)	7.1
18 (15)	ErbB-2 antagonist	97 (91)	10.3
19 (12)	DNA inhibitor	96 (106)	25.0
20 (16)	Glucocorticoid agonist	89 (88)	48.3
21 (23)	Microbiome modulator, live microorganisms	85 (70)	0.0
22 (17	Glucagon-like peptide 1 receptor agonist	82 (88)	12.2
23 (11)	Tumour necrosis factor alpha antagonist	81 (107)	33.3
24 (20)	Cell wall synthesis inhibitor	77 (77)	33.8
25 (34)	Cannabinoid receptor agonist	76 (52)	1.3

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

Source: Pharmaprojects®, January 2020

In a top 10 which hasn't changed much this year, other IO-related categories again put in a strong showing, with T cell stimulants growing by 77.7%, and Immune checkpoint inhibitors up by a rather more modest but still notable 23.5%. Just outside of the 10 is the first appearance of a newly created category for Gene editing. This technique is a type of genetic engineering in which DNA is inserted, deleted, modified or replaced at a precise location in the genome of a living organism. There are several different methods by which this is done, the highest profile of which is probably CRISPR. About a third of the drugs using gene editing techniques were identified within the past eight months, so although no therapeutics utilizing gene editing have yet moved beyond Phase II clinical trials, with 117 candidates already under development, this is clearly one hot potato.

Further immuno-oncology activity shows up in some of the table's high climbers. PD-L1 antagonists jump up the table following their 2019 debut, as, following initial successful launches, new candidates are poised to take a second bite at the cherry. But the category that's really full of beans this year is CD3 agonists, posting a 355% increase from 22 drugs last year to 100 this. CD3 is required for T-cell activation, and is under investigation for its ability to alter the co-stimulatory signal to help get the T-cell to recognize the cancer cell and become fully activated. As such, it is used by bispecific T cell engager (BiTE) drugs as their anchoring point to host T cells, and 2019 saw us classify this category against BiTE molecules more rigorously. BiTEs have now moved into three figures, so CD3 agonists are currently classified as under development as an IO strategy for more than 40 different kinds of cancer.

Another way to carve up the data on how drugs work is to look at the specific proteins which drugs target. This approach trims off the fat of the more general mechanisms which clog up Table 5, and gets straight to the meat of more precise targets. This is what Table 6 does, and it's an interesting mixture of the well-done and the rare. The prime cut this year is now Her-2, an established target, which knocks another even longer in the tooth target, the mu1 opioid receptor, off the top spot for the first time. It also marries up our number one disease with the number one target for the first time.

The top targets table usually moves fairly conservatively, but this year, there's an unusual degree of change. The CD3e molecule (target of the aforementioned CD3 agonists) zooms up the table, but its ascent is matched exactly by that of CD274, better known as PD-L1. With four drugs already on the market hitting CD274, it is the most successful IO-related target so far. Another target for IO, CD19, has more drugs in its pipeline and so is above it in our table, at number 5, but thus far the most advanced drug directly targeting CD19 is MorphoSys's tafasitamab, which is currently awaiting approval in the EU and US for relapsed or refractory diffuse large B-cell lymphoma. "CD19 is also the target for the vast majority of CAR-T therapies," notes Jonathan Stephens, Associate Director at Pharmaprojects and both an oncology and pharmacology expert. "There's a lot of these moving through early-stage development, and I don't see the trend of CD19 CAR-T going away any time soon." Elsewhere in the top 10, a fourth IO-related target – programmed cell death 1 (PD-1) – enters at number nine, while two traditional inflammation targets, the glucocorticoid receptor and cyclooxygenase-2, fall back. In today's landscape, these older categories are starting to look as old-fashioned as spam and powdered egg.

Table 6: Top 25 drug protein targets

Position 2020 (2019)	Target	No. of active compounds 2020 (2019)	Trend
1 (2)	erb-b2 receptor tyrosine kinase 2 *[Her-2]*	158 (135)	↑
2 (1)	opioid receptor, mu 1	148 (147)	↔
3 (5)	epidermal growth factor receptor	146 (121)	↑
4 (3)	vascular endothelial growth factor A	143 (131)	↔
5 (11)	CD19 molecule	121 (86)	↑↑
6 (14)	CD274 molecule	116 (76)	↑↑
7 (15)	CD3e molecule	116 (76)	↑↑
8 (6)	nuclear receptor subfamily 3, group C, member 1 *[glucocorticoid receptor]*	112 (113)	↔
9 (12)	programmed cell death 1	111 (86)	↑
10 (7)	prostaglandin-endoperoxide synthase 2 *[COX-2]*	107 (112)	↔
11 (4)	tumour necrosis factor	101 (123)	↓
12 (8)	insulin receptor	98 (104)	↔
13 (-)	cannabinoid receptor 1	97 (-)	↑↑
14 (10)	opioid receptor, kappa 1	97 (91)	↔
15 (9)	glucagon-like peptide 1 receptor	90 (94)	↔
16 (18)	membrane-spanning 4-domains A1	78 (72)	↔
17 (13)	prostaglandin-endoperoxide synthase 1 *[COX-1]*	76 (79)	↔
18 (16)	dopamine receptor D2	72 (74)	↔
19 (-)	transient receptor potential cation channel subfamily V member 1	69 (-)	↑↑
20 (-)	solute carrier family 6 member 2	65 (-)	↑↑
21 (-)	TNF receptor superfamily member 17	63 (-)	↑↑
22 (17)	gag-pol, HIV-1	61 (73)	↓
23 (19)	estrogen receptor 1	60 (62)	↔
24 (20)	adrenoceptor beta 2	57 (59)	↔
25 (23)	kinase insert domain receptor	57 (55)	↔

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

Source: Pharmaprojects®, January 2020

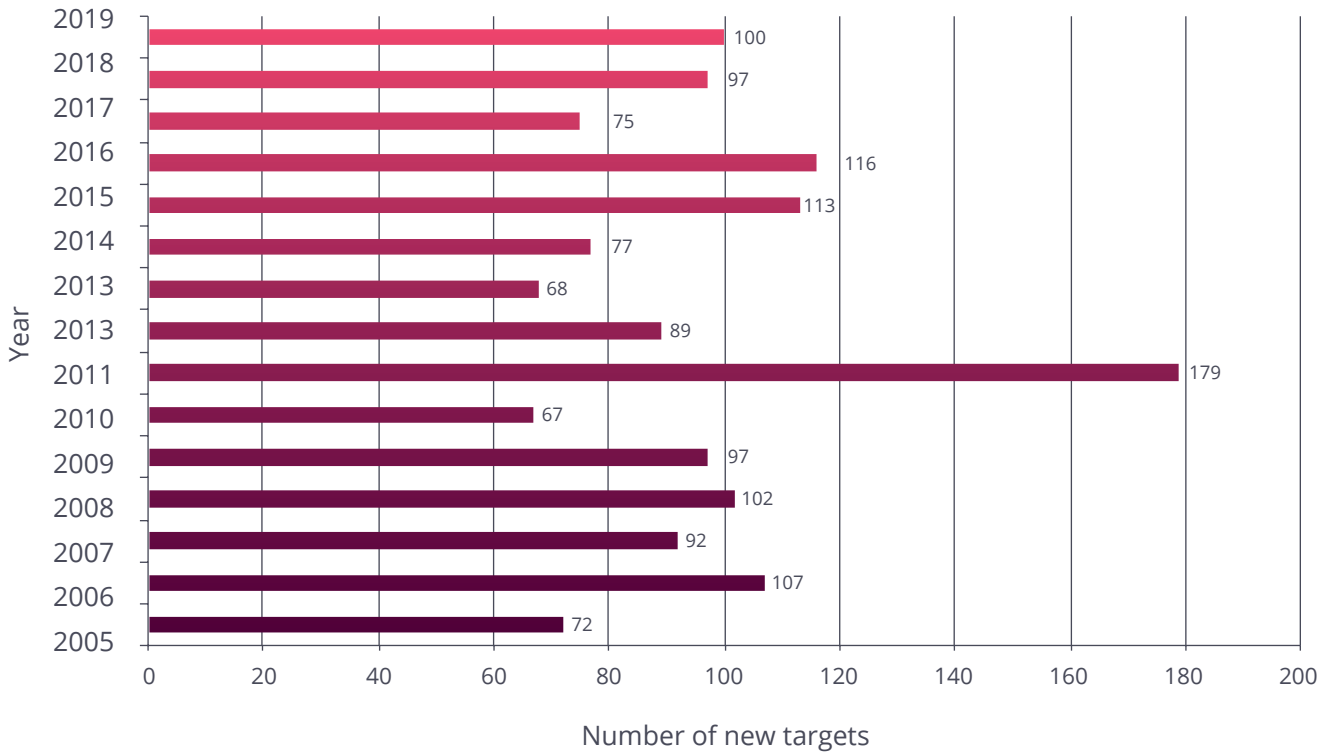
But it's not all about immuno-oncology. In at number 13 is the cannabinoid receptor, gaining traction on the basis of cannabinoids' increasing applications in a wide variety of diseases, from certain types of epilepsy and pain, to some cancers, inflammatory bowel disease, graft-versus-host disease, and even autism. Also targeting pain and joining the feast this year is transient receptor potential cation channel subfamily V member 1, in at number 19. This target, usually known by its more prosaic name of the vanilloid receptor 1, has a genuine food connection. It's the target for capsaicin and its derivatives, the ingredients which give chillies their heat. This agent has long been

known to have utility in post-herpetic neuralgia and neuropathic pain. Some cannabinoids hit this receptor too.

There are more new entries in the twenties, with solute carrier family 6 member 2, responsible for norepinephrine reuptake, flying the flag for neuroscience, while just below it is TNF receptor superfamily member 17. This is also known as BCMA, and is a prominent target for IO drugs in the form of antagonist MAbs, bispecifics, CAR-Ts and BiTEs.

Even in an industry which arguably has been underway for thousands of years, new foods emerge every year. Depending on which magazine think-piece you read, 2020's hot new foods could be pea milk, black tahini, or hemp hummus. Similarly, new drug targets emerge every year. In terms of brand-new drug targets during 2019, Figure 16 reveals that a nice round 100 were identified, again pretty much on the average for numbers seen in recent years. As long as we don't start seeing a decline in this metric, I think we can be satisfied that new ingredients to flavour drug R&D are still being discovered. The industry will be licking its lips at the news that, in tandem with this, the total number of targets which drugs are currently being actively developed against also rose this year, standing now at 1,766, up from 1,706. This number hasn't always gone up each year, so it is a very positive sign of progress.

Figure 16: Number of new drug protein targets identified by Pharmaprojects, by year



Source: Pharmaprojects®, January 2020

Dessert – Types of Pipeline Drugs
Biologicals have the sweet taste of success

Here comes the sweet trolley in our medicines meal, as we round off our review for 2020 by looking at the types of drugs in development, and the related topic of how they are administered. While chemical synthesis, the traditional medicinal chemistry way of making drugs, continues to be the industry's bread and butter, it has over the past couple of decades acquired a taste for biologicals. However, as Table 7 shows, the origin of most drugs in the pipeline in 2020 remains synthetic chemistry, with this category increasing its lead at the top of the table. It's worth noting though that this is also our 'default' category, applied to drugs in early development whose precise nature has not yet been disclosed.

The general category for monoclonal antibodies comes in second, and also posts an increase. Monoclonals are popular for their ability to precisely target bad apple disease-causing proteins, but they do have the disadvantages of usually being more expensive and needing to be given by injection. At number three, recombinant proteins take a bit of a dip, but at four, autologous cellular therapies (CAR-T and the like) are the cream in the process of rising to the top. Gene therapy's previously discussed advance is also reflected by the 19.2% increase in drugs which have the origin of nucleic acid delivered via viral vectors.

Table 7: Top 25 origins of pipeline drugs

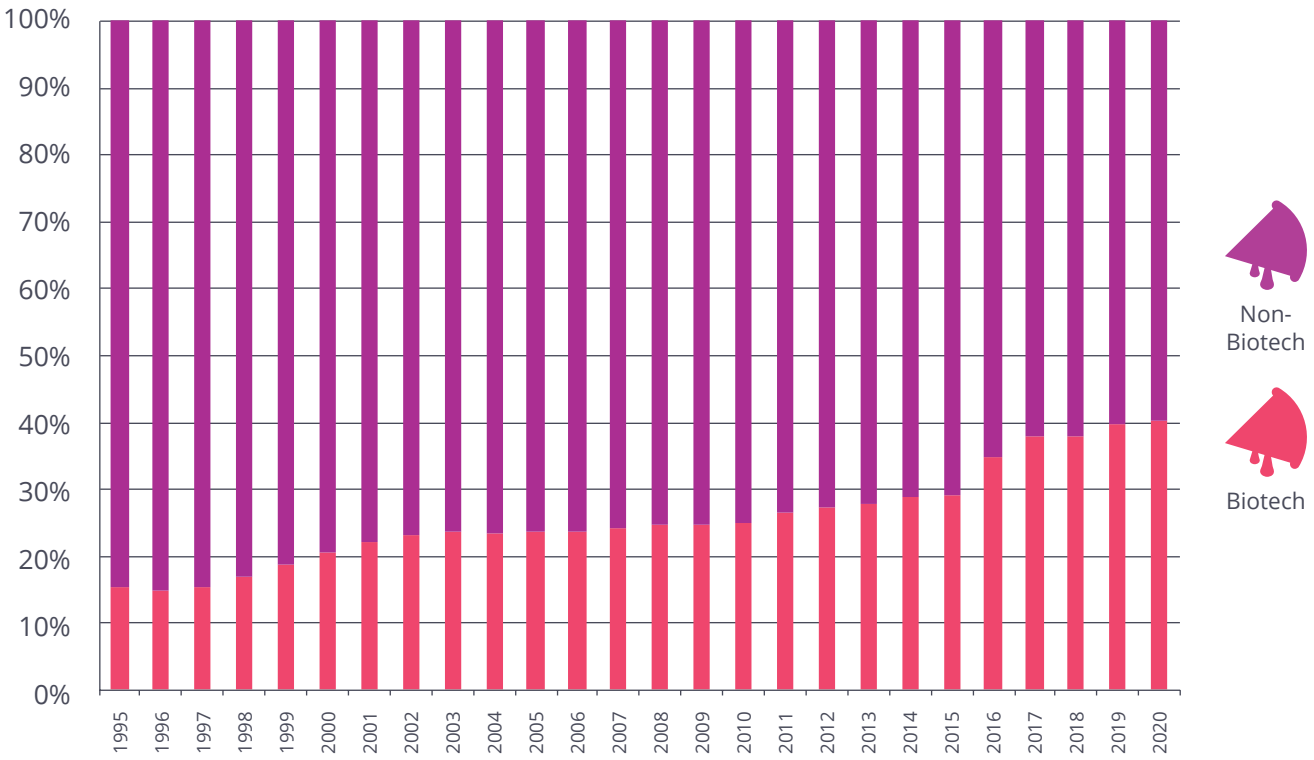
Position 2020 (2019)	Origin	No. of active products 2020 (2019)	Trend
1 (1)	Chemical, synthetic	8,921 (8285)	↑
2 (2)	Biological, protein, antibody	2,224 (2041)	↑
3 (3)	Biological, protein, recombinant	795 (840)	↓
4 (10)	Biological, cellular, autologous	602 (340)	↑↑
5 (4)	Biological, protein	549 (520)	↔
6 (7)	Biological, nucleic acid, viral vector	485 (407)	↑
7 (6)	Chemical, synthetic, peptide	478 (428)	↑
8 (5)	Biological, cellular	464 (512)	↓
9 (9)	Biological, virus particles	405 (373)	↑
10 (8)	Chemical, synthetic, nucleic acid	401 (392)	↔
11 (11)	Natural product, plant	306 (266)	↑
12 (14)	Biological, cellular, heterologous	302 (167)	↑↑
13 (12)	Biological, peptide	257 (248)	↔
14 (13)	Biological	245 (221)	↑
15 (15)	Biological, bacterial cells	218 (162)	↑↑
16 (16)	Biological, nucleic acid	205 (161)	↑
17 (17)	Biological, peptide, recombinant	147 (147)	↔
18 (18)	Biological, other	132 (106)	↑

Position 2020 (2019)	Origin	No. of active products 2020 (2019)	Trend
19 (19)	Biological, nucleic acid, non-viral vector	127 (102)	↑
20 (20)	Chemical, semisynthetic	61 (59)	↔
21 (22)	Natural product, bacterial	60 (43)	↑
22 (21)	Natural product	49 (45)	↔
23 (23)	Natural product, animal	34 (35)	↔
24 (24)	Natural product, fungal	29 (27)	↔
25 (-)	Chemical, synthetic, isomeric	21 (-)	↑

Source: Pharmaprojects®, January 2020

When breaking the entire pipeline down across the chemical/biological split, as Figure 17 does, we see that biologicals account for 40.4% of the pipeline now. Although this breaks through the 40% barrier for the first time, it does represent a slowing of the migration to biologicals, being just a 0.7% increase over 2019 (the previous year's rise was 1.8%). Is the march into biotech finally coming off the boil a bit?

Figure 17: Biological versus non-biological drugs as a percentage of the pipeline, 1995–2020

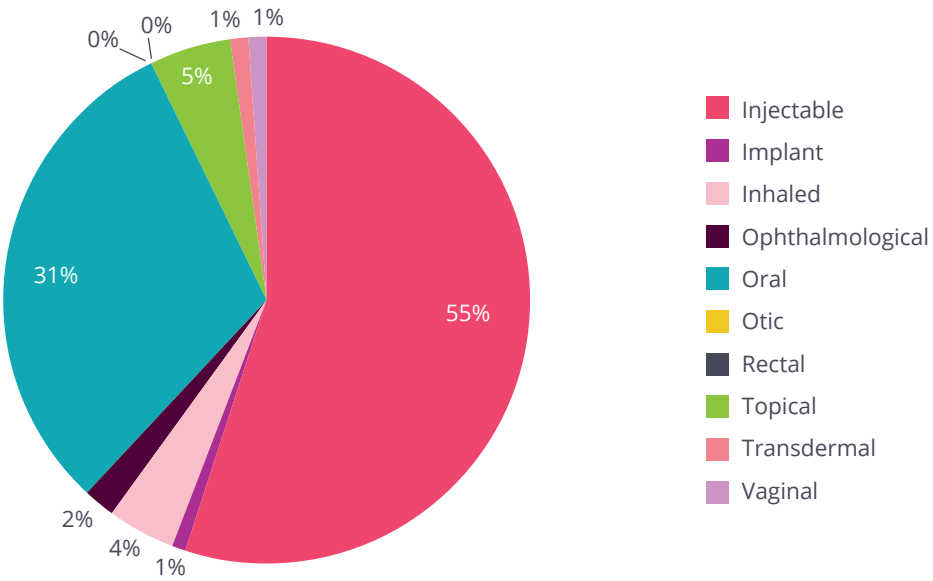


Source: Pharmaprojects®, January 2020

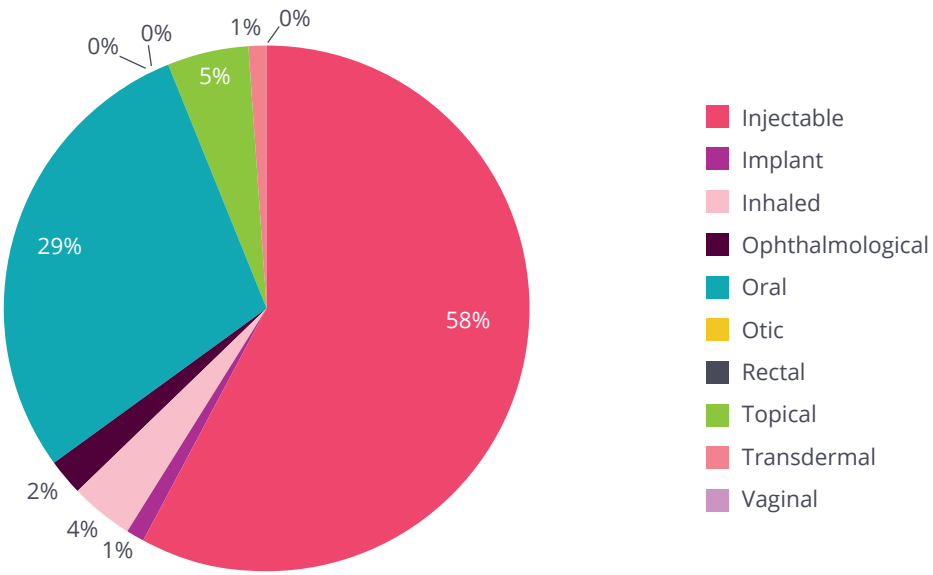
Despite this slight levelling off, there is a further increase in the proportion of drugs delivered by injection, as Figure 18 shows. Injectables rise from 55% to 58%, and there is a concomitant decline in the percentage of drugs taken orally, which falls by 2% to 29%.

Figure 18: Pipeline by delivery route, 2019 and 2020

2019



2020



Source: Pharmaprojects®, January 2020

Digestif – Plenty to gorge on, but will pharma suffer from indigestion?

So, as we round off our banquet with a digestif, how should we summarize the 2020 pharmaceutical R&D pipeline? Is it looking like a vintage year, or is there a concern that too many projects are still withering on the vine? To extend our viniculture-based metaphor, wines are generally assessed by five basic characteristics: sweetness, acidity, tannin, body, and alcohol. Undoubtedly, we have a full-bodied pipeline at present, with more candidates than ever before, hitting a wider range of targets. But preliminary data suggests the sweetness of successful novel drug launches was down through 2019. Will our pharma wine still have enough alcohol to have legs? Certainly, the acidic flavour of continued failure at Phase II has the potential to still leave a nasty taste in the mouth. But overall, 2020 is looking more like a glass half full than it is sour grapes.

At least with the increased focus on rare diseases, and immuno-oncology pushing new targets to the forefront of drug research, pharma R&D can't be accused of always trying to put new wine into old bottles. While there will always be something of a propensity in a high-risk industry to go for some low-hanging fruit, inarguably, the pipeline today looks far more 'innovative' overall than it did 20 years ago. Just think of all the 'new-world' varieties of drugs undergoing clinical development today: two decades ago, CAR-T, CRISPR, RNA interference, antisense, microbiome modulators, and even immuno-oncology were pretty much pie in the sky. Quoted in our sister-publication In Vivo[4], Michael Gilman, CEO of Arrakis Therapeutics, a firm developing small molecules to target RNA, said: "We're entering an era where it's becoming possible to 'drug the undruggable' – moving beyond the narrow range of targets accessible by conventional methods, and intervening in disease by reaching new drug targets with innovative drug discovery approaches." Another commentator in the same article, Bill Hinshaw, CEO of Axcella Health, highlighted the potential paradigm shift which is on the horizon. "We are now much more focused on developing treatments that reprogram or harmonize the body rather than suppressing or altering its functions," he notes. "As a result, there is an increasing transition from your standard small molecule regimens to new potential options like cell therapies, gene therapies and endogenous metabolic modulators." There is clearly potential for a bountiful harvest during the twenties.

So, the pharma field is flourishing with a wide variety of crops – but as with agriculture, sustainability is the key. As the global climate crisis accelerates, there is increasing pressure for us to change our eating habits. A UN Report from October 2019[5] proposed that, to keep temperature rises even under 2°C, the average world citizen needs to eat 75% less beef, 90% less pork, and half the number of eggs. Many advocate

4. In Vivo (2020) What Does 2020 Hold For Biopharma? Available from: https://invivo.pharmaintelligence.informa.com/IV124425/What-Does-2020-Hold-For-Biopharma [Accessed 31 January 2020].
5. Intergovernmental Panel on Climate Change (2019) Special Report Climate Change and Land. Available from: https://www.ipcc.ch/srccl/ [Accessed 14 February 2020].

a complete move over to veganism. One UK food success story was a beacon of hope during 2019: high street baking chain Greggs, known for its meat pies and bacon rolls, introduced, to much media amusement, a vegan sausage roll – and promptly posted a 13.5% increase in its sales. Pharma is of course itself a polluter, and a big one: a recent study found it to be a bigger CO2 emitter per dollar revenue than the automotive industry.

For pharma, the focus of sustainability is more about delivering a constant supply of new and improved products which benefit its consumers. It needs to deliver 50+ innovative medicines along the line of its own version of vegan sausage rolls every year: they too need to be attractive to consumers, a step forward, and affordable. Preliminary data, which will be presented in full in a supplement to this report that will be published a month hence, suggests that it only just met this goal in 2019. 2018 delivered a record-breaking 68 new active substances, which certainly won't be surpassed in the year just gone. But the reasons for this can be complex: a rash of approvals late in one year can leave the cupboard for another year looking disproportionately bare. We will examine last year's data and its context in more detail in our NAS supplement, but it should be noted that an apparently poorer performance in 2019 should not be allowed to sow the seeds of doubt about the industry's success. One rotten apple of a year should not be allowed to spoil the barrel.

The industry must be agile too, and respond quickly to emerging health threats. At the time of writing, the new coronavirus COVID-19, unheard of less than a month previously, is causing widespread international concern as Chinese and other authorities struggle to contain the spread of this unforeseen outbreak. While this could perversely offer a new opportunity for pharma (shares of Chinese R&D companies soared following its arrival), it does also show how quickly we can all be wrong-footed by nature. Despite all our efforts with irrigation, fertilizers and pest control, ultimately the harvest stands or falls by the weather, which we cannot control. Similarly, we can never know when new pathogens will emerge or become drug-resistant, when other environmental factors will increase disease incidence, or how changing human behaviours can affect prevalence (think the effect of the vaccine naysayers). Ultimately, mother nature is always going to be the smartest cookie in the jar.

Another variable it's hard to legislate for is political volatility. At the time of writing, the UK is just days away from staggering out of the EU like a drunk at closing time. While PM Boris Johnson won the recent election on a slogan of "Get Brexit Done" with his 'oven-ready' deal in place, the reality is that this is only the beginning – it could take up to a further 10 years to complete all of the

individual new trade negotiations that will need to be put in place. While leaving the EU doesn't seem to have adversely affected the UK's pharma industry as yet, none of this will be a piece of cake, and there is already talk of tit-for-tat taxes from Trump. Of course, it's election year in the US too, and it's as yet unclear which way the cookie will crumble there. With the rise of popularism across the world, trade wars, and a predicted global recession on the horizon, there's no shortage of potential obstacles peppering the path of pharma's progress which could leave the industry with a sore head.

But despite all this, 2020 sees the pharma industry looking well fed and in rude health. It has most of the ingredients it needs to cook up an exciting menu of new dishes, and, increasingly, the right recipes too. So, as we come to the end of our data banquet this year and work out how to split the check, let's raise a final glass to pharma and its continued success. And here at Pharmaprojects, like any good restaurant critic, we will continue to taste the goods, track their progress from farm to fork, and keep our consumers apprised of who's producing the caviar and who's just serving up chicken nuggets. Cheers!

About the Author

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Ian Lloyd is the Senior Director of Pharmaprojects and Data Integration, overseeing the content and analyst services for our drug development solution. He supports clients in their drug pipeline data requirements and inquiries, providing insight into the best search strategies to answer their drug-related business questions and also identifying and analyzing trends in pharma R&D. For over 25 years, he has authored the “Pharma Annual R&D review” and its new active substances (NAS) launches supplement. This has become a must-have industry report for those seeking to identify the changing fortunes of drug R&D. Ian joined Pharmaprojects in 1987, when it was part of PJB Publications. It was acquired by Informa in 2003. He previously worked in molecular biology as a research assistant at the University of Bristol.

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