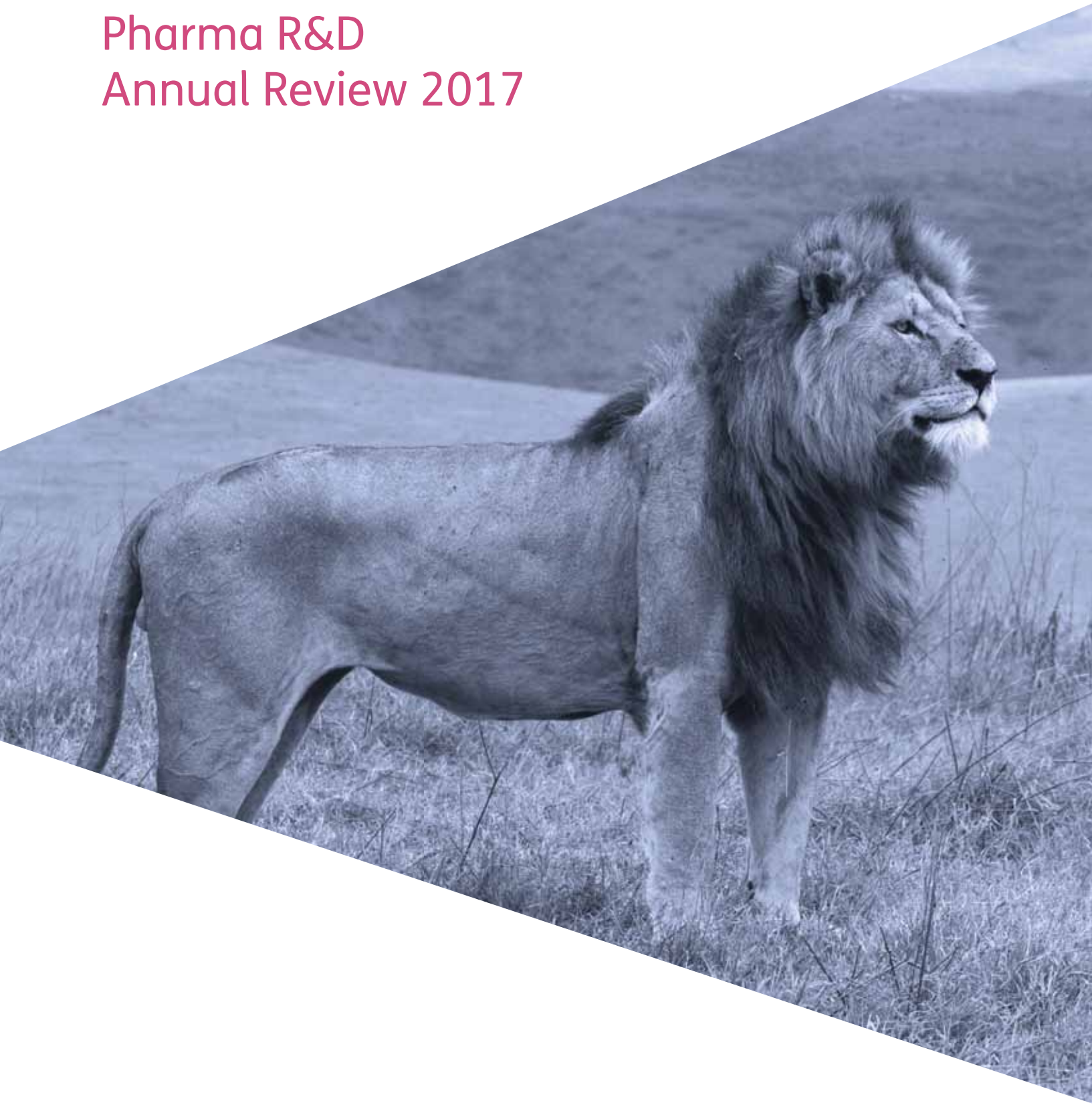
Pharmaprojects
Pharma intelligence | informa

Pharma R&D Annual Review 2017



Ian Lloyd, Senior Director
Pharmaprojects & Data Integration

Introduction

Welcome to Pharmaprojects' 2017 review of trends in pharmaceutical R&D. For around 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 how the land lies at the start of 2017. We'll assess industry trends by examining the pipeline by company, therapeutic area, disease, target and drug type, using data from Pharma Intelligence's Phamaprojects, 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 past. But here, we will be focusing on research and development as it is now, how it is changing and mutating, and where it has been headed during 2016.

2016, with the benefit of very near hindsight, looks to have been a momentous year for the world at large – and not necessarily all in good ways. Leaving aside the wailing and gnashing of teeth at the seemingly endless parade of celebrity deaths which swept across social media almost daily, and the ongoing unspeakable humanitarian disaster of the Syrian civil war, two democratic rabbits out of hats will undoubtedly change the fortunes of many for a generation. Few foresaw the UK's Brexit vote, and many still cannot quite believe that Donald Trump is the US President. Whatever your views on these events, they unarguably have changed the direction of travel for most of the world, and will have wide-reaching consequences for us all. While it's too early to detect their influence on pharma R&D, few would argue that that they won't have any effect.

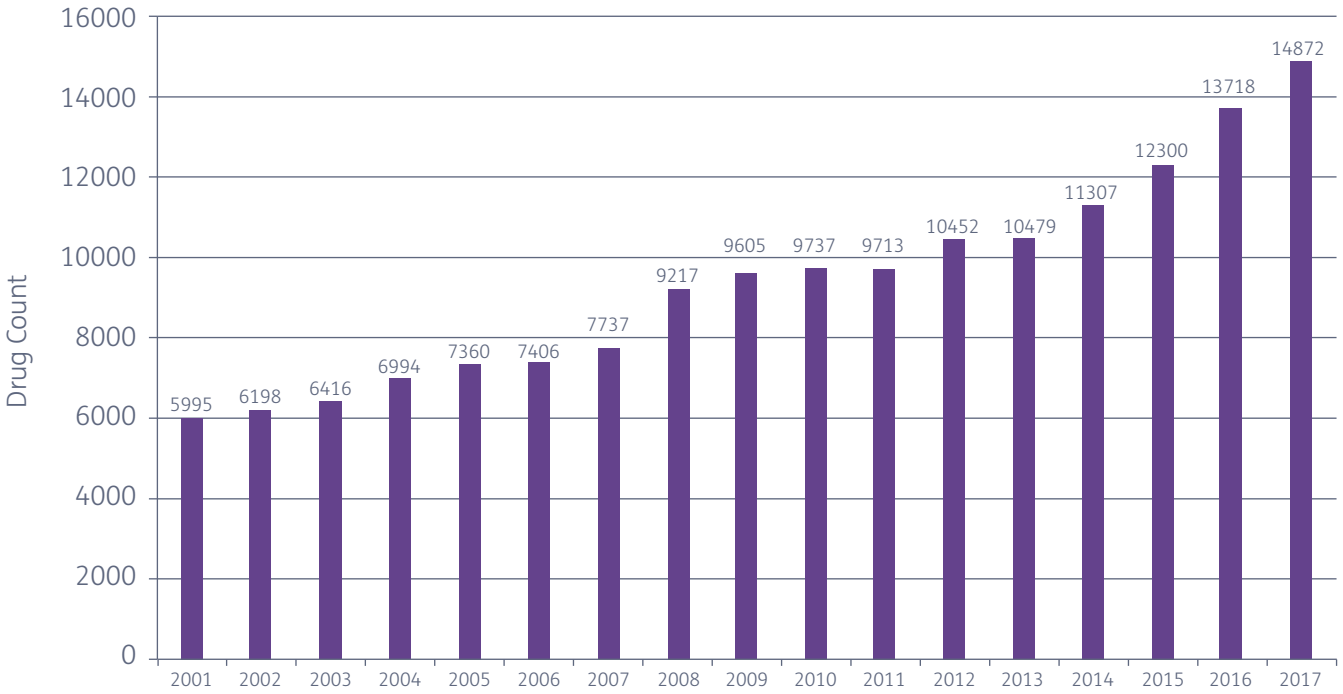
So in a world where it sometimes felt that the humans were making rather a hash of things, some sought solace last year in the somewhat purer motivations of the animal kingdom. In the UK, the highest rating TV programme in 2016 (leaving aside, as I feel we should, a rather eccentric local show about, ahem, baking cakes), was not a sports event, a royal wedding, or a soap opera death, but a beautiful nature documentary featuring snow leopards. British audiences swooned over the BBC's latest wildlife documentary series, *Planet Earth II*, helmed as ever by the comforting presence of 90-year old Sir David Attenborough, venerated throughout the realm as broadcasting royalty. This six-part televisual treat was stuffed with truly jaw-dropping footage: goats clambering up sheer vertical cliffs, wild Mustang stallions fighting to gain control of a Nevada waterhole and its associated females, rhesus macaques free-running their way across the buildings and roofs of Jaipur to conduct dawn raids on food from the local street market, and tiny glass frogs defending their eggs from attacking wasps by delivering a sharp boot to the face. Each film was full of astounding footage of amazing animals doing extraordinary things, and couldn't help but leave its audience in a state of perpetual wonder.

Whilst reminding us, as a climate change sceptic takes office as leader of the free world, what an amazing and precious world we are lucky to share in, I couldn't help but be struck by some parallels from the show in how the natural world functions and the machinations of our own little biosphere, the pharmaceutical industry. Our habitat has limited resources, but a growing population of differing creatures all vying for their share. Some animals are naturally top of the food chain, but need to constantly compete to stay pack leaders. Meanwhile, there is huge biodiversity at the other end of the scale, but many of our smaller community members continually face the risk of extinction, or of being gobbled up by their larger neighbours. And everyone is looking for that unique property which will give it an evolutionary advantage or its own niche. So let us venture, bullwhip and fedora in-hand, Indiana Jones-style, into the pharma jungle, and marvel at the creatures lurking there and the strategies which they are employing to not only survive, but to proliferate.

Total pipeline size – The pharma forest is teeming with life

We are starting our zoological survey as always by taking a complete census of the pharma biosphere. Figure 1 shows the total number of drugs in the R&D pipeline as of January 2017, and how this has changed since the start of the century. 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 in still in development for additional indications or markets.

Figure 1: Total R&D Pipeline Size by Year 2001-2017



Source: Pharmaprojects®, January 2017

This year's figure is a massive 14,872 pipeline projects, an increase of 8.4% on the corresponding figure from 2016. And as the graph clearly shows, this continues the steep upward climb seen over the past five years. However, it is worth noting that the rate of increase has slowed somewhat – it was 11.5% through 2015-16, and 8.8% the previous year. But I think it's a little early to suggest that the pipeline population is about to peak. Just as one swallow does not make a summer, a slight slowdown over one year doesn't necessarily indicate that resource constraints are starting to have an effect on restricting pipeline expansion. But it certainly makes next year's figure an intriguing prospect.

Ultimately, any biological entity exists to produce offspring, and in the pharmaceutical industry, perhaps its 'children' are new drug launches. If it doesn't successfully and continually bring new and innovative entities to the market, the organization must gradually become moribund, affecting its ability to continue to fund innovative R&D. In other words, the pipeline cannot expand indefinitely if its end products start to diminish.

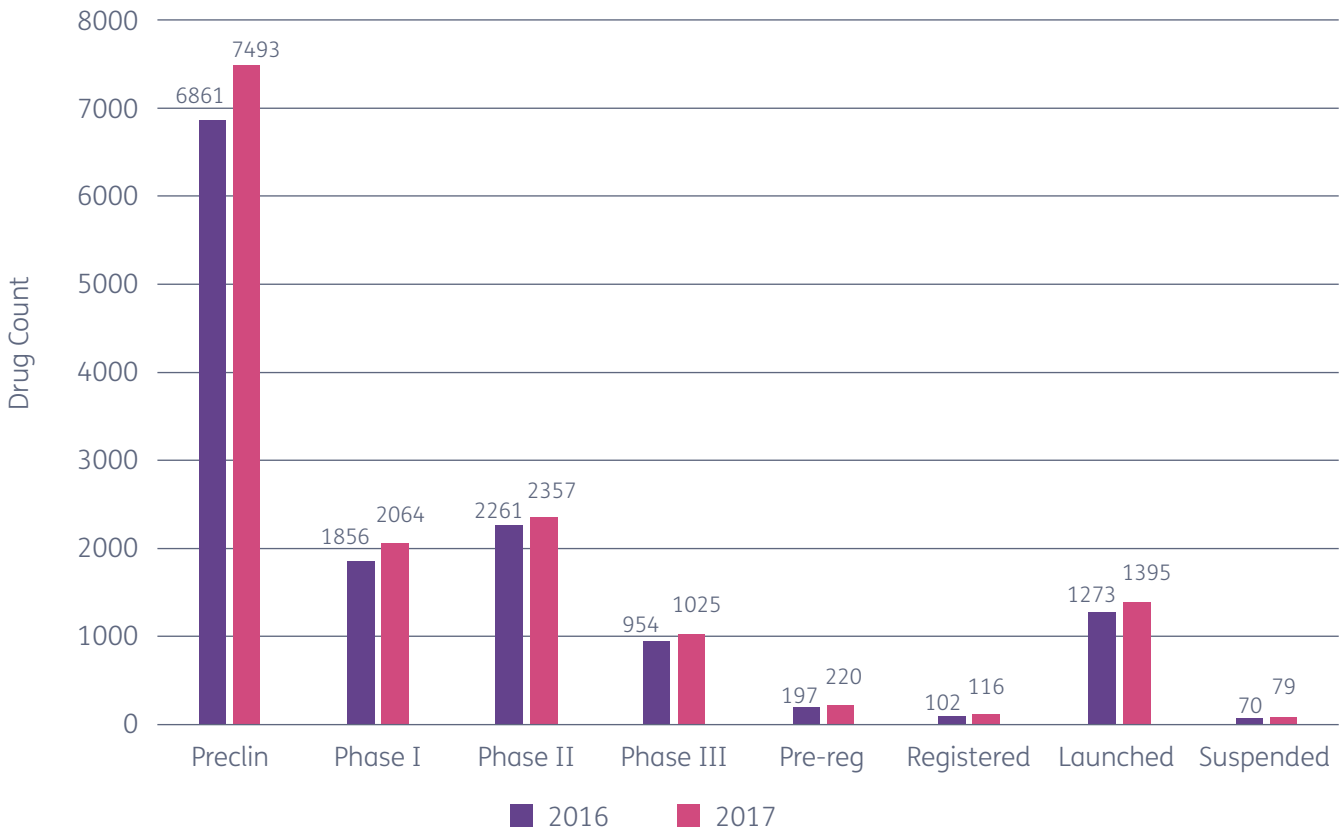
It's therefore interesting to note that the rate of pipeline expansion fell back a little following a year where the number of new active substance (NAS) launches was lower than the preceding year (46 in 2015 vs 63 the previous year). The NAS number for

2016 is still being finalized at the time of writing, but it will certainly be lower still than that in 2015. Are we beginning to see the fall in pharma's birth rate starting to peg back its population growth? All the animals in pharmaland are depending on new drug launches to replenish their ecosystem, otherwise they will find they start to compete more heavily for dwindling resources. Check back in the spring for our NAS supplement to see which way the wind is blowing.

The 2017 pipeline by phase – Baby boom leads the way, but growth throughout the family

Whatever the long-term fate of the size of the pharma pipeline, it's encouraging to see that the 8.4% growth is spread once again across all development phases. Figure 2 compares the number of drugs at each stage of development with the equivalent data for last year. The greatest growth occurred at the preclinical stage, with an extra 632 hatchlings joining the brood of early drug candidates, a rise of 9.2%. But there are increases across the board throughout the clinical and later regulatory phases, which suggests that the pipeline colony as a whole is flourishing.

Figure 2: Pipeline by Development Phase 2017 vs 2016

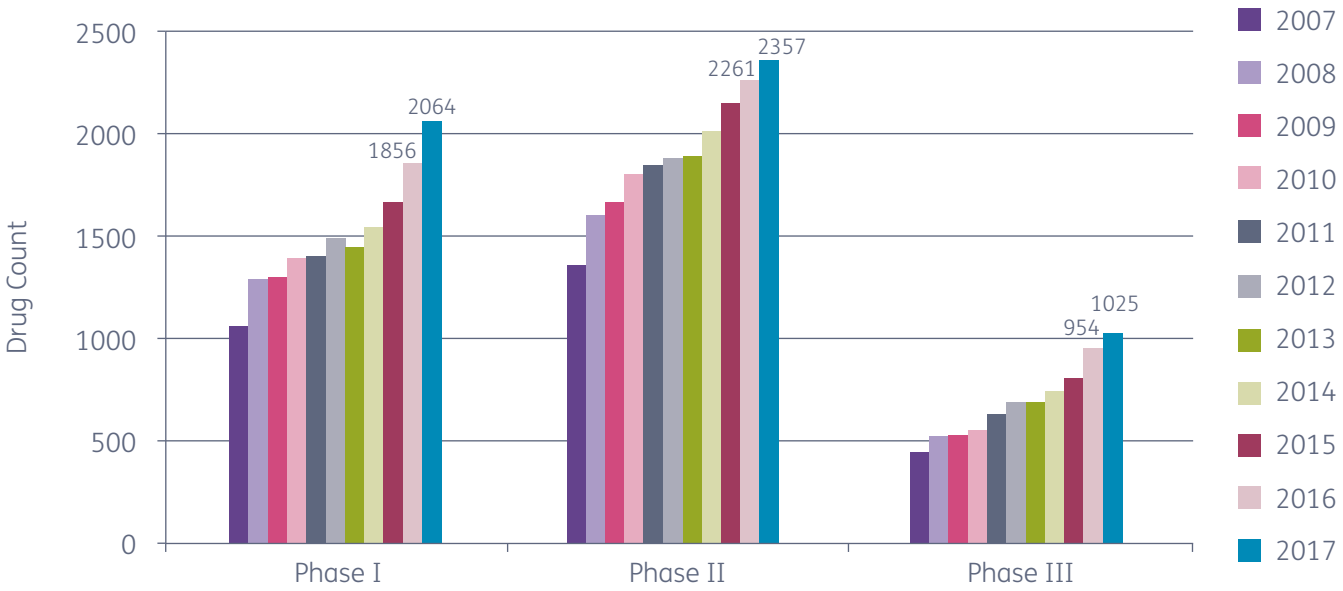


Source: Pharmaprojects®, January 2017

Preclinical figures will always be more difficult to gauge accurately, but due to the need to register trial protocols with relevant authorities, data is very robust across the clinical phases. So perhaps one of the best measures of pipeline health is looking at the herd migrating through the challenging terrain of clinical trials. Here, we can take a longer view back across a decade, to examine population growth in this most important family of drugs.

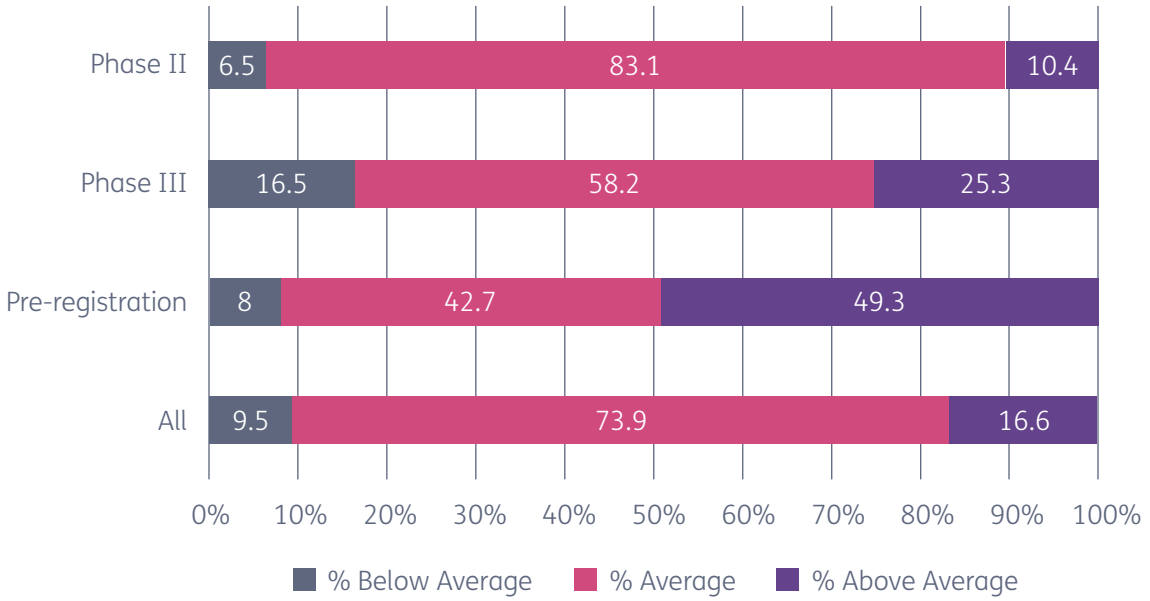
As Figure 3 shows, while there were increases in the numbers of drugs at every clinical phase, this year, Phase I saw the greatest rise, with the number of candidates at this first stage in humans increasing by an impressive 11.2%. This number is now at almost twice the number of that seen ten years ago. The corresponding values for Phase II and Phase III are 4.2% and 7.4%, respectively. While increases in clinical candidate numbers are generally to be welcomed, there are two caveats. One, all of these increase rates are lower than those seen a year ago, the Phase III figure considerably so (it rose by 18.1% last year). Two, clinical trials are a cost. Unless they are leading to new drug progeny, they are simply using up the valuable and limited resources of the pharma ecosystem.

Figure 3: Clinical Phase Trends 2007-2017



Source: Pharmaprojects®, January 2017

Figure 4: Distribution of Likelihood of Approval Ratings for Pipeline Drugs in Phase II to Pre-registration*



** The Likelihood of Approval (LOA) represents the probability of reaching FDA approval from a current phase. The average is calculated for a specified disease group based on the historical performance of drugs within the same disease group and development phase.*

Source: Biomedtracker, January 2017

So if the population counts of our pipeline animals are looking good, what about their chances of survival? After all, there are plenty of examples in the natural world of species which produce large numbers of offspring in the knowledge that predation or starvation is going to lead to a high attrition rate. To take a view on the current pipeline's quality, we reviewed some data from our sister product, Biomedtracker. Biomedtracker's analysts examine clinical and regulatory events in order to place their own weighting on a drug's likelihood of approval by the FDA. Figure 4 represents this data for products in the Phase II, Phase III or Pre-registrational phases of development, showing the % of drugs at each phase that have a higher than average, average, or lower than average chance of making it to the market.

This shows some encouraging news for the late stage pipeline, with almost half of drugs awaiting approval rated as having a better than average chance of making it to adulthood. This figure drops to about a quarter when we look at the candidates in Phase III, but this still compares favourably with the 16.5% rated as have a lower than average likelihood of approval at this development stage. So the lifecycle of the R&D ecosystem appears to be in rude health, both in terms of the numbers of its creatures and the chances of them making it to maturity.

Top companies – Big beasts still dominate, but Novartis is the new king of the jungle

Let's move to look at the beasts which inhabit our pharma jungle, the pharmaceutical and biotech companies themselves. Table 1 lists the Top 25 biggest companies by size of R&D pipeline. It seems that GlaxoSmithKline (GSK) has this year lost its position as the king of the jungle, losing out to Novartis by just a single project. The Swiss conglomerate's ascendancy to pole position is compounded by the fact that it originated a greater proportion of its pipeline itself compared to GSK. But the latter will not be licking its wounds too much, having grown its own pipeline and strengthened its pre-eminence as the UK's pharma leviathan – nearest rival AstraZeneca falls back this year. Pfizer continues its bounce back up in the Top 10[1], in which Johnson & Johnson, AstraZeneca, Roche and Sanofi all showed actual declines in the numbers of drugs in their pipelines. And the most notable feature of the Top 10 is that its members have not changed at all. There were no large extinction events in pharma in 2016 and on your safari, you'll be seeing the same big beasts as last year.

Table 1: Top 25 Pharma Companies by Size of Pipeline

Position 2017 (2016)	Company	No of Drugs in Pipeline 2017 (2016)	No of Originated Drugs 2017
1 (2)	Novartis	251 (240)	161
2 (1)	GlaxoSmithKline	250 (242)	149
3 (6)	Pfizer	232 (217)	148
4 (5)	Merck & Co.	229 (223)	141
5 (4)	Johnson & Johnson	214 (227)	111
6 (3)	AstraZeneca	213 (231)	119
7 (7)	Roche	206 (211)	129
8 (8)	Sanofi	193 (199)	80
9 (10)	Bristol-Myers Squibb	144 (136)	105
10 (9)	Takeda	141 (137)	80
11 (11)	Eli Lilly	126 (124)	95
12 (12)	Allergan	122 (119)	60
13 (13)	Bayer	112 (111)	77
14 (14)	Daiichi Sankyo	105 (102)	62
15 (15)	Astellas Pharma	104 (95)	59
16 (19)	AbbVie	102 (90)	39
17 (18)	Amgen	94 (91)	65
18 (28)	Shire	93 (57)	34
19 (20)	Boehringer Ingelheim	88 (88)	66
20 (21)	Eisai	87 (88)	52
21 (16)	Otsuka	86 (94)	45

1 Pfizer previously held the top position in 2011, but since then, its ranking had consistently slipped until recently.

22 (17)	Teva	82 (92)	44
23 (22)	Celgene	76 (67)	32
24 (26)	Valeant Pharmaceuticals	72 (59)	34
25 (45)	Ligand	66 (38)	20

Source: Pharmaprojects®, January 2017

However, there has already been acquisitive activity in the Top 10 since these figures were produced, with the announcement in January 2017 that Johnson & Johnson (J&J) is to acquire Actelion, following a protracted on-off courtship that had Sanofi as a rival suitor at one point. Actelion currently has 24 drugs in its pipeline, but the deal is complicated by the fact that its Phase II and below pipeline will be spun off into a separate company, in which J&J will have a minority stake. Nevertheless, J&J should be feeling confident that it has already staked its claim to be in 2018's Top 10 companies.

Further down the chart, we do see a couple of examples of conspicuous consumption via differing strategies. Shire moves up the charts, preferring to swallow whole with its acquisition of Baxalta. But Ligand clawed its way into the Top 25 using a licensing strategy; the company has a plethora of deals, and is notable for having the highest proportion of non-self-originated drugs in the Top 25 in its portfolio. There are three companies making a Phexit from the table this year: Gilead Sciences, which slipped down to 27, despite slightly growing its pipeline; and the Japanese concerns Mitsubishi Tanabe and Sumitomo Dainippon, which fell back to numbers 28 and 31, respectively, but are hardly looking like becoming endangered species. However, this chart doesn't tell the whole story. While there may not be many examples of big M&A activity akin to the famed internet meme of a snake swallowing a crocodile, there is plenty of hunting and consuming of smaller prey going on. In one of *Planet Earth II's* most memorable and oft-repeated sequences, newly-hatched baby marine iguanas sought to make their way across a Galapagos Island beach to the relative safety of the seashore and their as-yet unmet parents. But lurking in the shadows in the crevices of the rocks are racer snakes. These nightmarish serpents seek to smother the baby lizards as they sprint seaward, hunting in packs, coming from all sides, and piling in on their victims at the end-game. The plucky little iguanas seem to have not much chance to make it alone, and a very short life-expectancy.

It's always tempting to anthropomorphize and root for the plucky prey to resist the claws and jaws of those at the top of the food chain. But as the series' commentary frequently reminds us, if that lioness fails to kill the cute fluffy antelope, it is she and her cubs who will starve. This is the law of the jungle. While it might be somewhat extreme to extend this analogy wholly to the pharma industry, in recent years, it seems to have become a fact of life that the only way in which the big beasts can survive is by consuming some of the tasty baby critters which come their way. Examples of small acquisitions numbered almost 100 during 2016, and those joining in the feeding frenzy included Pfizer (acquiring Bamboo Therapeutics, Anacor and Medivation), Merck & Co (Iomet and Afferent), Bristol-Myers Squibb (Padlock Therapeutics and Cormorant) and AstraZeneca (Acerta). Of course, where our animal analogy breaks down is that many of these lower order organisms went all too willingly to their deaths – it might be the only way in which they could ensure that their baby drugs have a future – or that their fat cat investors get their paydays.

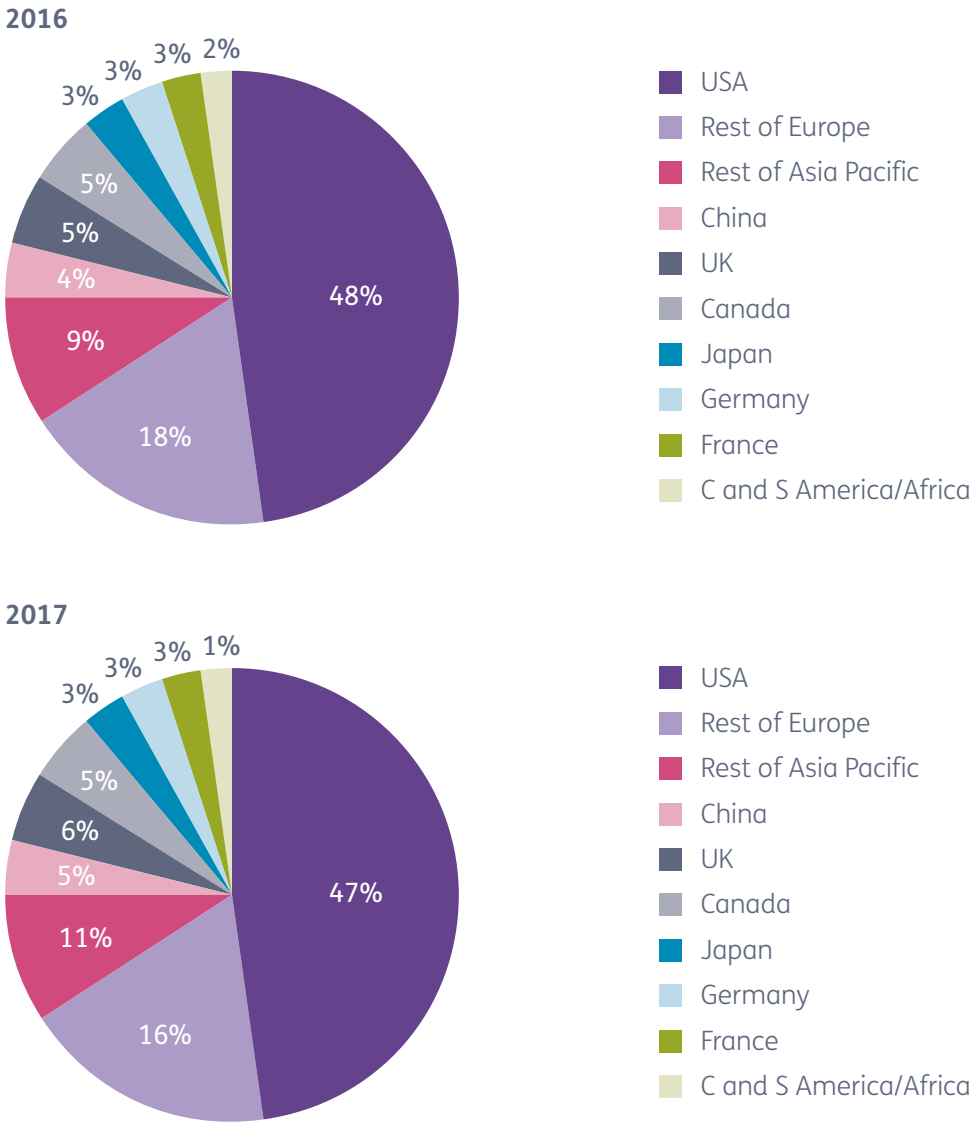
Despite the voracious appetites of those at the top of the food chain, the growth in biodiversity appears to know no bounds. Almost 750 new companies were identified and added to the Pharmaprojects database over the past twelve months – a staggering birth rate, and a significant uptick from the 618 seen in both preceding years. However, company acquisitions, and more pointedly, company deaths or hibernations, meant that the total number of active companies grew by less than half this figure. As of January 2017, as Figure 4 depicts, 4,003 pharma firms were reporting active pipelines, an increase of 8.6%. Once again, this is lower than the 2015-16 number (12.2%), but is still a strikingly large growth rate. Clearly, venture capital funding is far from being an endangered species. The pharma minnows continue to proliferate, with 1,578 companies having just a single product in their pipelines, and 679 with two. Like krill, these tiny creatures nevertheless contribute a sizeable 56.4% of the pharma company biomass – a percentage virtually unchanged this year.

Figure 5: Total Number of Companies with Active Pipelines 2001-2017

Source: Pharmaprojects®, January 2017

What is the geographical distribution of the pharma flocks? Well they certainly seem to be continuing to migrate eastwards. Asian firms now account for 19% of companies, up from 16% last year, and driven not only by further expansion in China, but also by general growth throughout the region. This has come at the expense of Europe and the US, which both fall back by 1%, although the latter still accounts for almost half of all R&D companies worldwide. Keen Breixiteers will no doubt be heartened by the UK taking its share up from 5% to 6%, and it will be interesting the track this metric over the coming years. Evolution on isolated islands has historically been noted for throwing up some strange beasties!

Figure 6: Distribution of R&D Companies by HQ Country/Region 2016 and 2017



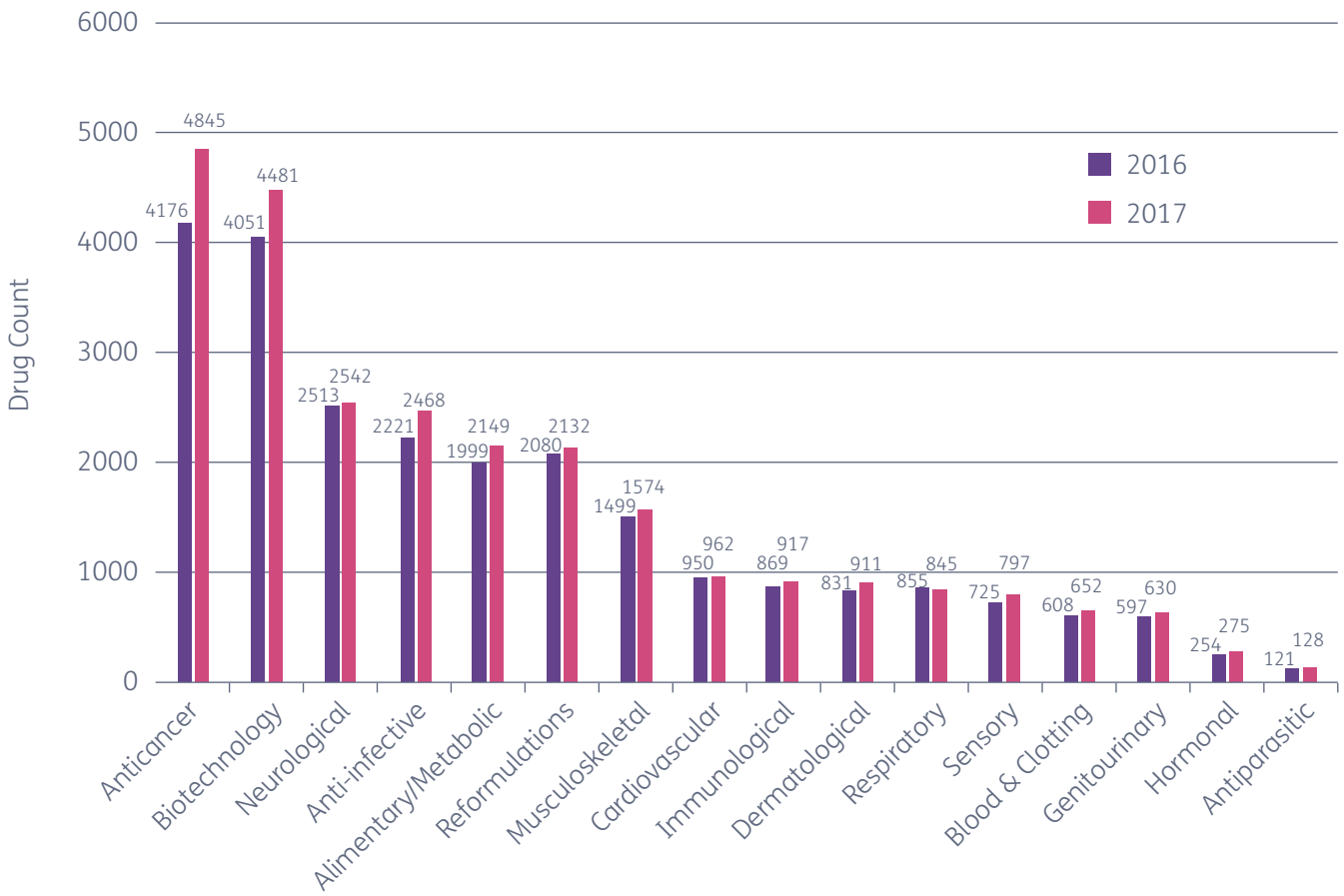
Source: Pharmaprojects®, January 2017

Top therapies – Cancer's herds spread further into the pharma habitat

We now move to looking at the therapeutic focus of the R&D pipeline, akin to assessing pharma's habitat and seeing which species are growing and what competitors this might be at the expense of. Figure 7 looks at this at the family level, counting up the numbers of drugs in each broad therapeutic group.

It seems that, more than ever before, there are herds of cancer drugs sweeping majestically across the pharma plain. The population of Oncological therapeutics has shot up far faster than the pharma average, increasing its citizenry by 669 candidates, a growth rate of 16.0%, even just surpassing last year's record-breaking 15.9% rise. This puts it in 2017 growing at almost twice the rate of the pipeline as a whole, and taking a 32.6% share of the pie – almost a third. For the first time, there is perhaps a hint that others being squeezed out by this unchecked expansion – the Respiratory group actually posts a decline this year. Elsewhere, some other expansion rates are pegged back, with Neurologicals only up by 1.2% and Musculoskeletals by 5.0%. Nevertheless, Alimentary/Metabolic drugs increased by a % close to the average, and Anti-infectives actually also beat the mean with an 11.1% rise. So while there is no sign of cancer drugs becoming the dominant lifeform just yet, they continue their stealthy and predatory advance, munching through gradually increasing amounts of the pharma forest's natural resources.

Figure 7: The R&D Pipeline by Therapy Group



Source: Pharmaprojects®, January 2017

This becomes more apparent when we move to the genus level – the individual 232 therapeutic categories which comprise Pharmaprojects' therapeutic classification – the Top 25 of which can be seen in Table 2.

Table 2: Top 25 Therapeutic Categories

Position 2017 (2016)	Therapy	No of R&D Products 2017 (2016)	Trend
1 (1)	Anticancer, other	2231 (2071)	↑
2 (2)	Anticancer, immunological	2001 (1597)	↑
3 (3)	Prophylactic vaccine, anti-infective	848 (729)	↑
4 (4)	Antidiabetic	624 (592)	↔
5 (5)	Ophthalmological, other	615 (546)	↑
6 (10)	Monoclonal antibody, other	589 (432)	↑
7 (14)	Gene therapy	547 (417)	↑
8 (6)	Anti-inflammatory	513 (475)	↔
9 (11)	Antiviral, other	488 (424)	↑
10 (9)	Immunosuppressant	478 (437)	↔
11 (7)	Reformulation, fixed-dose combinations	457 (473)	↔
12 (8)	Recombinant vaccine	437 (469)	↓
13 (13)	Cognition enhancer	430 (419)	↔
14 (18)	Neurological	426 (388)	↑
15 (12)	GI inflammatory/bowel disorders	422 (424)	↔
16 (17)	Musculoskeletal	417 (401)	↔
17 (19)	Biosimilar	417 (386)	↑
18 (15)	Monoclonal antibody, human	414 (412)	↔
19 (16)	Analgesic, other	409 (403)	↔
20 (20)	Cardiovascular	408 (375)	↔
21 (23)	Reformulation, other	400 (325)	↑
22 (22)	Monoclonal antibody, humanized	377 (345)	↔
23 (21)	Recombinant, other	358 (349)	↔
24 (27)	Anticancer, vaccine	332 (306)	↑
25 (24)	Antiparkinsonian	318 (321)	↔

Source: Pharmaprojects®, January 2017

The general cancer category stays top of the tree with a 7.7% increase, but this is dwarfed by the 25.3% growth in numbers of immunological anticancers, which are now snapping at its heels. The latter's rise is driven by the new breed of immuno-oncology drugs, as we will see later. Elsewhere, Gene therapy, which a few years ago, if not exactly an endangered species, was certainly looking to be in terminal decline, experienced a second straight year of population explosion, growing its pack size by 31.2% on the back of a 41.8% expansion last year. We can see that both prophylactic vaccines and antivirals contributed to the anti-infective renaissance. But the general cell therapy category dropped out of the Top 25, being replaced by anticancer vaccines.

We can further break down our pharma zoo by going to the species level – the individual diseases for which drugs are in development. The Top 25 for this classification – which now has over 1,350 different members – is shown in Table 3.

Table 3: Top 25 Diseases/Indications

Position 2017 (2016)	Disease*	No. of Active Drugs 2017 (2016)	Trend
1 (1)	Cancer, breast	654 (614)	↑
2 (2)	Cancer, lung, non-small cell	477 (452)	↔
3 (3)	Cancer, colorectal	476 (431)	↑
4 (4)	Cancer, pancreatic	416 (431)	↔
5 (5)	Diabetes, Type 2	415 (386)	↑
6 (7)	Cancer, ovarian	386 (374)	↔
7 (8)	Alzheimer's disease	376 (374)	↔
8 (6)	Arthritis, rheumatoid	372 (378)	↔
9 (9)	Cancer, prostate	362 (365)	↔
10 (11)	Cancer, brain	322 (287)	↑
11 (10)	Cancer, melanoma	312 (298)	↔
12 (17)	Cancer, leukaemia, acute myelogenous	285 (232)	↑
13 (14)	Psoriasis	283 (257)	↑
14 (12)	Pain, nociceptive, general	268 (278)	↔
15 (15)	Cancer, liver	264 (241)	↑
16 (13)	Asthma	254 (273)	↓
17 (19)	Cancer, myeloma	246 (218)	↑
18 (16)	Parkinson's disease	246 (236)	↔
19 (18)	Cancer, head and neck	227 (221)	↔
20 (20)	Cancer, lymphoma, non-Hodgkin's	217 (216)	↔
21 (21)	Cancer, gastrointestinal, stomach	213 (196)	↔
22 (23)	Cancer, renal	197 (186)	↔
23 (22)	Chronic obstructive pulmonary disease	192 (190)	↔
24 (24)	Infection, HIV/AIDS	183 (185)	↔
25 (25)	Pain, neuropathic, general	169 (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 2017

Several species of cancer drugs dominate the landscape, taking seven of the top ten slots and nine of the top twelve. Breast cancer is the most common condition which drugs are seeking to treat, posting a 6.5% pipeline expansion, similar to that seen with colorectal at number 3. Non-small cell lung cancer at 2 grows more modestly, and pancreatic cancer at 4 fell back a little following a big rise in 2016. The highest climber in percentage terms is acute myelogenous leukaemia, which received a 22.8% boost to its troupe size. Losing out in the Top 25, which has exactly the same populace as last year, were asthma and HIV/AIDS, both of which posted small declines.

Types of pipeline drugs – As biologicals proliferate, is the small molecule becoming a dinosaur?

From the therapeutic focus of the pipeline, we switch to the kinds of drugs which are in research and development, and how they have been produced. This is tracked by Pharmaprojects' Origin of Material field, and how the pipeline breaks down according to this index is detailed in Table 4.

Table 4: Top 25 Origins of Pipeline Drugs

Position 2017 (2016)	Origin	No of Active Drugs 2017 (2016)	Trend
1 (1)	Chemical, synthetic	7,855 (7,540)	↑
2 (2)	Biological, protein, antibody	1,687 (1,466)	↑
3 (3)	Biological, protein, recombinant	861 (892)	↔
4 (4)	Biological, protein	545 (439)	↑
5 (5)	Chemical, synthetic, peptide	468 (434)	↑
6 (6)	Biological, virus particles	367 (303)	↑
7 (10)	Biological, cellular	352 (210)	↑
8 (8)	Biological, nucleic acid, viral vector	329 (297)	↑
9 (7)	Chemical, synthetic, nucleic acid	323 (301)	↔
10 (9)	Biological, cellular, autologous	251 (214)	↑
11 (12)	Biological, peptide	226 (178)	↑
12 (11)	Natural product, plant	198 (198)	↔
13 (13)	Biological	181 (143)	↑
14 (16)	Biological, bacterial cells	135 (108)	↑
15 (18)	Biological, nucleic acid	130 (97)	↑
16 (14)	Biological, cellular, heterologous	129 (137)	↔
17 (17)	Biological, peptide, recombinant	124 (107)	↔
18 (20)	Biological, other	112 (64)	↑

19 (15)	Biological, nucleic acid, non-viral vector	110 (126)	↓
20 (19)	Chemical, semisynthetic	62 (69)	↔
21 (23)	Natural product, bacterial	45 (43)	↔
22 (22)	Natural product	44 (45)	↔
23 (24)	Natural product, animal	37 (37)	↔
24 (25)	Chemical, synthetic, isomeric	28 (34)	↓
25 (26)	Natural product, fungal	27 (20)	↑

Source: Pharmaprojects®, January 2017

As ever, the Chemical, synthetic category, which is applied to most small molecules (and is the default for drugs of unknown origin) is way out in front of this chart. But on closer inspection, its expansion rate is just 4.2%, well below the rate for the pipeline as a whole. Contrast that with the runner-up category, antibodies: this class of drugs rose by a striking 15.1%. Elsewhere in the table, other biological classes fare similarly well, with general categories for biological proteins, cellular therapies and peptides up 24.1%, 67.1% and 27.0%, respectively, and similar increases for some of the more specific biological subclasses (the origin classification has three levels of hierarchy). So are biologicals stealthily mounting a takeover and making small molecules start to seem like dinosaurs?

There's no mass extinction event underway for sure, but there are signs of biologicals starting to outcompete their indigenous neighbours. Of course, there are plenty of examples in the natural world of new interlopers squeezing out original inhabitants. Us Brits like to cite the example of the North American grey squirrel, the 'rat with a fluffy tail' which, once introduced to our shores, systematically took over from our own indigenous (and much prettier) red squirrel, which now clings on only in Northern Scotland, while the grey runs riot in every urban back garden. Could biologicals simply be better adapted to today's climate and perform a similar usurpation?

One way to see this more clearly is by tracking how the pipeline is split across biotech and non-biotech drugs, and this is what we've done in Figure 8. This year's graph gives the clearest indication yet that the industry is involved in transferring a significant proportion of its eggs into the biotech basket.

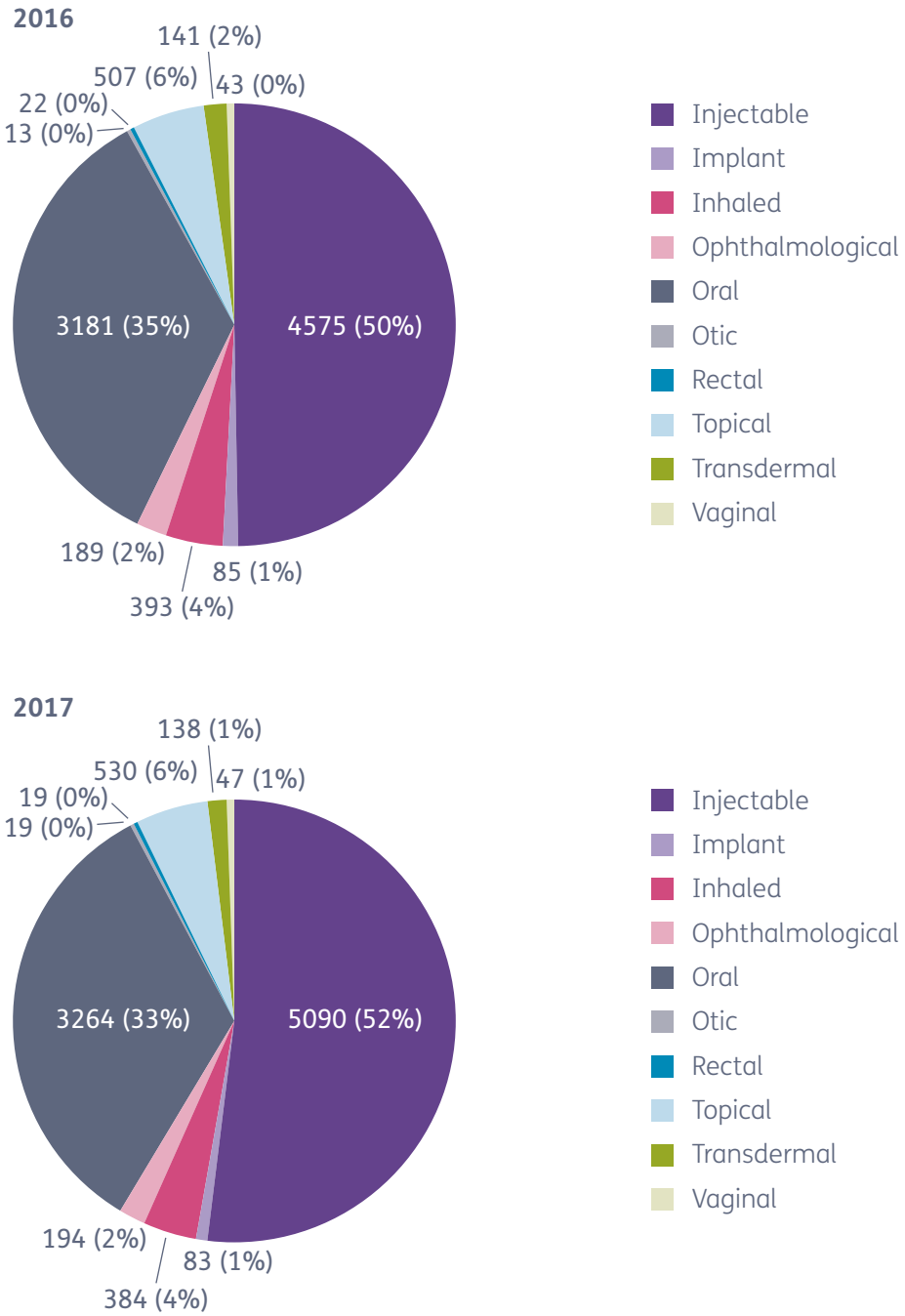
Figure 8: Biological vs Non-biological Drugs as a Percentage of the Pipeline 1995-2017

Source: Pharmaprojects®, January 2017

The proportion of pipeline drugs which can described as biotech-based in 2017 has reached 37.8%, and there has been a definite acceleration in the upwards trend over the past few years. But new chemical entities are not set to be dodos; there is surely a place for small molecules in the future, although where the set point is between the two competing species remains to be seen. Biologicals can bring better efficacy and specificity, but often at the price of less convenient delivery, side-effects, and of course, higher cost.

How this shift towards biologicals is starting to affect how drugs are delivered to patients can be investigated by breaking down the pipeline by delivery route, and this is what Figure 8 does, comparing again data for 2016 with now. Not surprisingly, this data follows suit, with an increase in the percentage of drugs delivered by injection from 50% to 52% over the past twelve months. There is a concomitant decline by 2% of oral drugs, with the %s for other more minor delivery routes unchanged. This demonstrates that the move to biologicals must still be accompanied by more parenteral delivery, as most macromolecules still have to be delivered in this less attractive way.

Figure 9: Pipeline by Delivery Route 2016 & 2017



Source: Pharmaprojects®, January 2017

Mechanisms and Targets – how to stay alive in a crowded ecosystem

In a crammed environment like a rainforest, with competition for resources and many competitors and predators, animals have evolved many extraordinary and often unique strategies to maintain their niches and gain an advantage. Similarly, pharma and biotech companies must continually innovate in their R&D programmes to stay ahead of the game. So let's now move to looking at their biology, and the mechanisms of action and targets which they are investigating to produce new and excitingly diverse novel drugs.

Table 5 first shows the Top 25 mechanisms of action being utilized. It's worth noting here that again this classification in Pharmaprojects is hierarchical. Since a drug's precise mode of action may not be disclosed or identified during the earliest stages of development, this naturally means that the higher level, broader categories are favoured, being only later replaced with more precise MOAs. This explains why the Top 10 contains so many general categories such as Immunostimulant, Immunosuppressant, Angiogenesis inhibitor and Apoptosis inhibitor.

Two years ago, Anticancer immunotherapy was added as a new category to cover the then emerging field of immuno-oncology (IO) drugs, and encompass a number of related strategies. Looking at Table 5 today, it would seem that 2016 was the year that immuno-oncology emerged from its pupal stages into the light as a fully-fledged butterfly. It shows a phenomenal 123% increase in the number of drugs which can be categorized in this way over the past 12 months, up from 399 in Jan 2016 to 889 in Jan 2017. Although the IO field in truth contains a bit of a mixed bag of differing individual strategies, it's unprecedented to see an area grow so much over such a short time. Only 19% of drugs with this tag are launched, approved or awaiting approval at present, but if more move forward successfully and growth continues at this rate, this is one island which could become overcrowded very quickly.

Table 5: Top 25 Mechanisms of Action (Pharmacologies)

Position 2017 (2016)	Mechanism of Action (Pharmacology)	No. of Active Compounds 2017 (2016)	% of Compounds PR/R/L
1 (1)	Immunostimulant	1736 (1704)	15.0
2 (2)	Anticancer immunotherapy	889 (399)	2.1
3 (3)	Immunosuppressant	215 (221)	27.4
4 (4)	Angiogenesis inhibitor	179 (181)	19.0
5 (9)	Vascular endothelial growth factor (VEGF) receptor antagonist	123 (103)	15.4
6 (8)	DNA inhibitor	120 (107)	20.0
7 (5)	Apoptosis stimulant	115 (132)	18.3
8 (7)	Tumour necrosis factor alpha antagonist	114 (110)	24.6
9 (6)	Opioid mu receptor agonist	114 (130)	41.2
10 (10)	Cyclooxygenase 2 inhibitor	102 (102)	38.2
11 (11)	Glucocorticoid agonist	95 (99)	34.7

12 (13)	T cell stimulant	87 (75)	5.7
13 (14)	Glucagon-like peptide 1 agonist	84 (75)	13.1
14 (12)	DNA topoisomerase II inhibitor	81 (84)	27.2
15 (18)	Gene expression inhibitor	74 (69)	-
16 (15)	Cyclooxygenase 1 inhibitor	72 (73)	44.4
17 (22)	ErbB-2 antagonist	71 (64)	14.1
18 (20)	Cell wall synthesis inhibitor	69 (65)	31.9
19 (17)	DNA synthesis inhibitor	67 (71)	26.9
20 (19)	Insulin secretagogue	67 (67)	47.8
21 (16)	T cell inhibitor	66 (72)	21.2
22 (34)	Histone deacetylase inhibitor	59 (51)	8.5
23 (23)	Tubulin inhibitor	58 (58)	12.1
24 (32)	HMGCoA reductase inhibitor	58 (51)	25.9
25 (26)	Cell cycle inhibitor	57 (58)	31.6

**Abbreviations used in Table: PR/R/L = Pre-registration/Registered/Launched*

Source: Pharmaprojects®, January 2017

Elsewhere in this particular Top 25, there is little to remark on, with not a lot of movement in the table, and most categories just adding a few candidates. Perhaps more insight can be gleaned by looking at the top targets for drug development, so Table 6 lists the 25 proteins most commonly targeted by drug R&D. It's interesting to note that the IO mechanism category is so diverse that no individual IO-specific targets yet make the Top 25.

Table 6: Top 25 Drug Protein Targets

Position 2017 (2016)	Target	No. of Active Compounds 2017 (2016)	Trend
1 (1)	opioid receptor, mu 1	143 (156)	↔
2 (2)	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	123 (127)	↔
3 (3)	tumour necrosis factor	123 (109)	↔
4 (5)	erb-b2 receptor tyrosine kinase 2 *[Her-2]*	113 (105)	↔
5 (4)	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) *[COX-2]*	106 (106)	↔
6 (9)	vascular endothelial growth factor A *[VEGF-A]*	105 (80)	↑
7 (6)	epidermal growth factor receptor	104 (103)	↔
8 (8)	insulin receptor	94 (88)	↔
9 (7)	opioid receptor, kappa 1	87 (91)	↔
10 (14)	glucagon-like peptide 1 receptor	82 (72)	↑
11 (12)	dopamine receptor D2	79 (73)	↔
12 (11)	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) *[COX-1]*	75 (75)	↔
13 (10)	polyprotein, hepatitis-C virus	75 (78)	↔
14 (13)	adrenoceptor beta 2, surface	74 (73)	↔
15 (15)	gag-pol, HIV-1	68 (67)	↔
16 (18)	estrogen receptor 1	62 (57)	↔
17 (27)	amyloid beta (A4) precursor protein	61 (50)	↑
18 (16)	opioid receptor, delta 1	60 (64)	↔
19 (22)	membrane-spanning 4-domains, subfamily A, member 1 *[CD-20]*	60 (53)	↑
20 (19)	angiotensin II receptor, type 1	57 (56)	↔
21 (20)	progesterone receptor	57 (56)	↔
22 (26)	3-hydroxy-3-methylglutaryl-Coenzyme A reductase	56 (51)	↔
23 (21)	androgen receptor	55 (53)	↔
24 (17)	tubulin, beta class I	55 (62)	↓
25 (25)	topoisomerase (DNA) II alpha 170kDa	54 (51)	↔

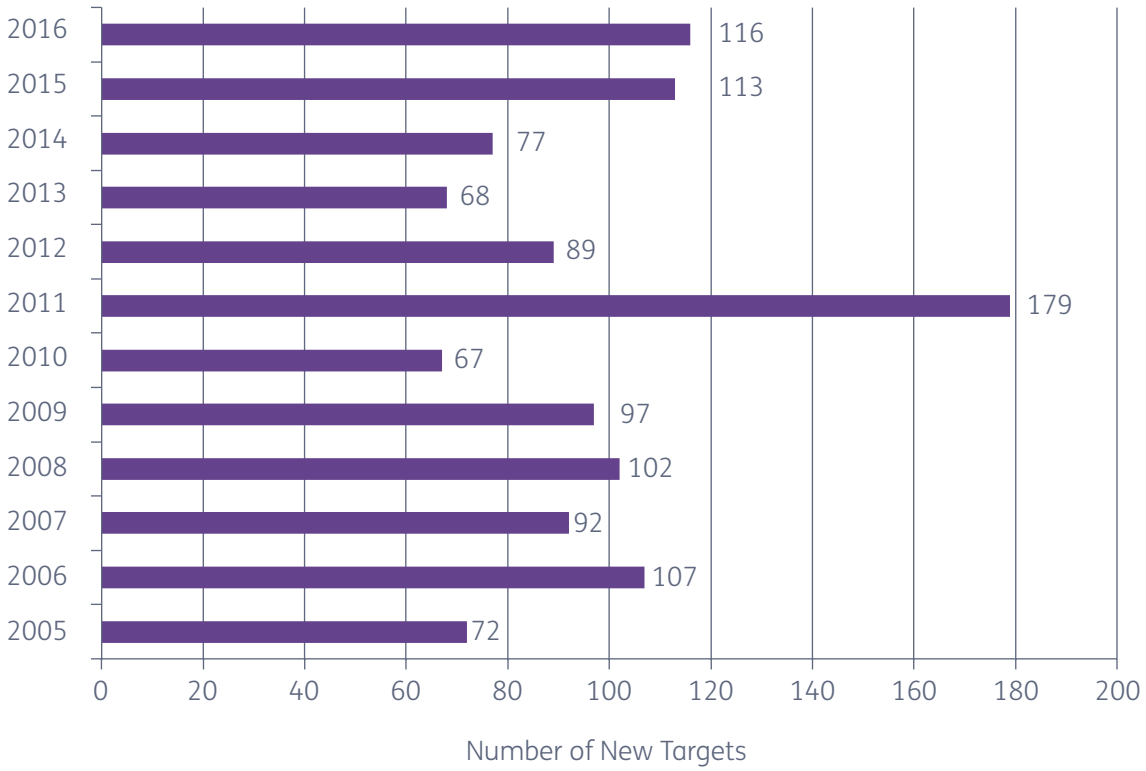
NCBI names, except additions it italics made by us for clarity

Source: Pharmaprojects®, January 2017

In fact, it's still a pain target, the mu opioid receptor, which sits atop this particular tree, where it is joined in the Top 10 by the related kappa 1 receptor and several targets involved in inflammation. There are some individual cancer targets also there, with a notable increase for VEGF-A, up over 30% and climbing to number 6. Another interesting climber is amyloid beta (A4) precursor protein, up 10 places to 17. This is a target in the therapy of Alzheimer's disease, an area which had another rocky year in 2016, with solanezumab joining the elephant's graveyard of high profile failures in Phase III trials (although at the time of writing, Lilly had yet to confirm its final discontinuation). There is still considerable controversy as to the veracity of the amyloid hypothesis in the pathology of the disease, so a few eyebrows may be raised in some quarters at this evidence that the industry is still investing heavily in it.

Overall, our data shows that in the current R&D pipeline, 1,672 individual proteins are being targeted by drugs, and the cumulative number for all time is now up to 2,774. This means that over the course of the past 12 months 116 brand new targets for drug development were identified for the first time (incidentally a similar figure to the number of new animal species discovered by zoologists during the year). This ranks 2016 a much better than average year in terms of target innovation (see Figure 10).

Figure 10: Number of New Drug Protein Targets Identified by Pharmaprojects by Year



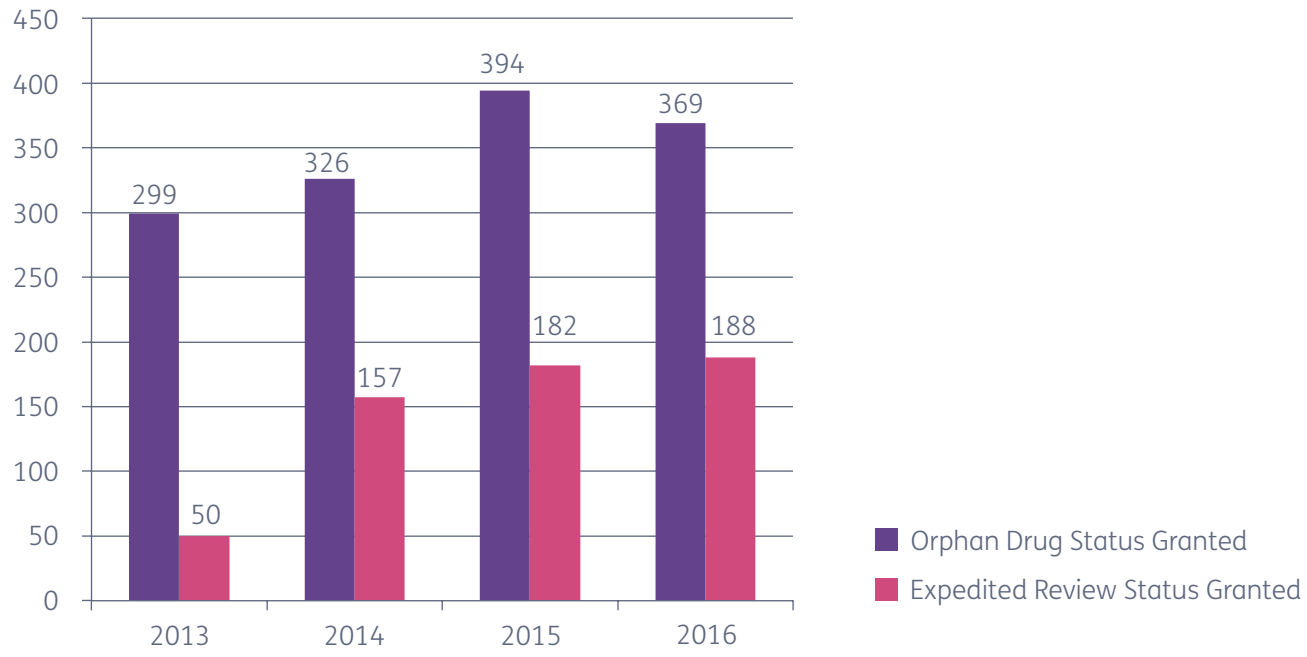
Source: Pharmaprojects®, January 2017

Survival of the fittest – Darwinian forces mean pharma's creatures must find their niches

So it would seem that, for yet another year, the take-home message on pharma R&D can be summed up most simply as: there's more of it than ever. If pharma is like an ecological habitat, it must surely still be more of a rainforest than a desert, as it is certainly diverse and teeming with life. Rainforests currently cover just 6% of the Earth's landmass, but contain over 50% of its species. But the maintenance of all environments requires care and planning. Currently, it is estimated that more than 150 acres of Amazon rainforest is lost every minute of every day, equating to 78 million acres lost every year. More than 20% percent of the Amazon rainforest is already gone, and with it, we are losing 137 plant, animal and insect species every single day. That adds up to 50,000 species a year. This makes attrition rates for drugs seem like more of a walk in the park.

But let there be no doubt that selection pressures will increasingly exert their power with Darwinian ferocity in the pharma jungle. Here, as in a real jungle, it's all about finding a niche. One of the ways in which the industry has been doing this is by focusing on rare diseases or diseases with great unmet need. A way of gaining a survival advantage if you're working in these areas is to utilize the orphan drug status programmes available in a number of markets, or to use the various expedited review designations which can speed approval, such as fast-track status and breakthrough designation. This was still a popular strategy during 2016, although as Figure 11 shows, there were slightly fewer orphan drug statuses granted than during the previous year.

Figure 11: Rise in Numbers of Drugs Receiving Orphan Drug Status or an Expedited Review Designation* 2013-2016



**Data for 2013 not complete as we only began systematically recording the dates of these events mid-year. Figure includes designations granted in the United States, European Union, Australia/New Zealand, Japan, South Korea and Mexico.*

Source: Pharmaprojects®, January 2017

So rare diseases still seem to be very much in vogue, whilst the light for immuno-oncology, spurred on by some notable successes, seems to be burning ever brighter. But the industry needs to keep focus and not be overly dazzled by the latest shiny things. *Planet Earth II* again has a salutatory lesson from the animal kingdom. In another memorable sequence, newly-hatched baby turtles, which normally head for the sea guided by the full moon, became distracted by lights from the nearby town instead, and headed disastrously the wrong way up the beach. Many, instead of reaching a rich life in the open seas, instead were destined to be squished by traffic on the beachside road. Pharma must similarly not become distracted, and has to focus on ensuring it is travelling in the right direction. Incidentally, in this case, following transmission, it was revealed that the film crew broke their 'non-intervention' rule on this occasion and rescued the turtles headed the wrong way. Unfortunately, we can't expect our politicians and regulators to perform similar acts of mercy!

In fact, it's entirely possible that President Trump might hurl a meteorite of changes in regulation or pricing controls at the pharma world and cause, if not a mass extinction event, at least some seismic changes in pharma. We will have to wait and see. Sometimes the world changes despite the views of those in charge – for instance, it was recently confirmed that 2016 was the warmest year that planet Earth has yet experienced.

Ultimately, for any species to survive, it must continue to produce viable progeny. That's what we'll be looking at when we return in a month's time with our Annual Review NAS Supplement, examining the first-time drug launches of 2016. Early indications are that it was not a vintage year, and that fact might ultimately apply the brakes to unfettered pipeline population growth more than anything else in the end. But there is little sign as yet of anything upsetting the harmony in the pharma biosphere. The Gaian hypothesis proposes that the Earth itself is a dynamic system of living organisms and inorganic material which work to maintain the Earth as a fit environment for life. Is the same true for pharma? Will it prosper whatever is thrown at it, or is it a fragile ecosystem whose life is forever teetering on the edge of disaster. Whatever the outcome, Pharmaprojects and the rest of Informa's Pharma Intelligence will be tracking trends and giving you the evolutionary advantage of clear, unbiased information and insight.

Pharma intelligence
informa

pharma@informa.com

United States
52 Vanderbilt Avenue
11th Floor
New York
NY 10017
USA
+1 646 957 8919
+1 888 436 3012

United Kingdom
Christchurch Court
10-15 Newgate Street
London
EC1A 7HD
United Kingdom
+44 20 7017 5000

Japan
Kotakudo Ginza
Building, 7th Floor
5-14-5 Ginza
Chuo-ku
Tokyo
104-0061
+81 351 487 670

China
23rd Floor
China Online Centre
333 Lockhart Road
Wanchai
Hong Kong
+85 239 667 222

Australia
Level 7
120 Sussex Street
Sydney
NSW 2000
+61 2 8705 6900

Informa's Pharma intelligence is home of the world's leading pharma and healthcare R&D and business intelligence brands – Datamonitor Healthcare, Sitetrove, Trialtrove, Pharmaprojects, Medtrack, Biomedtracker, Scrip, Pink Sheet, In Vivo. Pharma intelligence's brands are trusted to provide over 3000 of the world's leading pharmaceutical, contract research organizations (CRO's), medical technology, biotechnology and healthcare service providers, including the top 10 global pharma and top 10 CRO's, with an advantage when making critical R&D and commercial decisions.

Accurate and timely intelligence about the drug development pipeline is vital to understanding the opportunities and risks in today's biopharmaceutical marketplace – whether you are targeting an unmet medical need, investigating promising new therapies or researching drug development historical trends and treatment patterns. If you are providing contract research or other services in the pharma industry, you need to stand out. A solid understanding of your potential clients' pipelines and competition will help you leave a lasting impression.