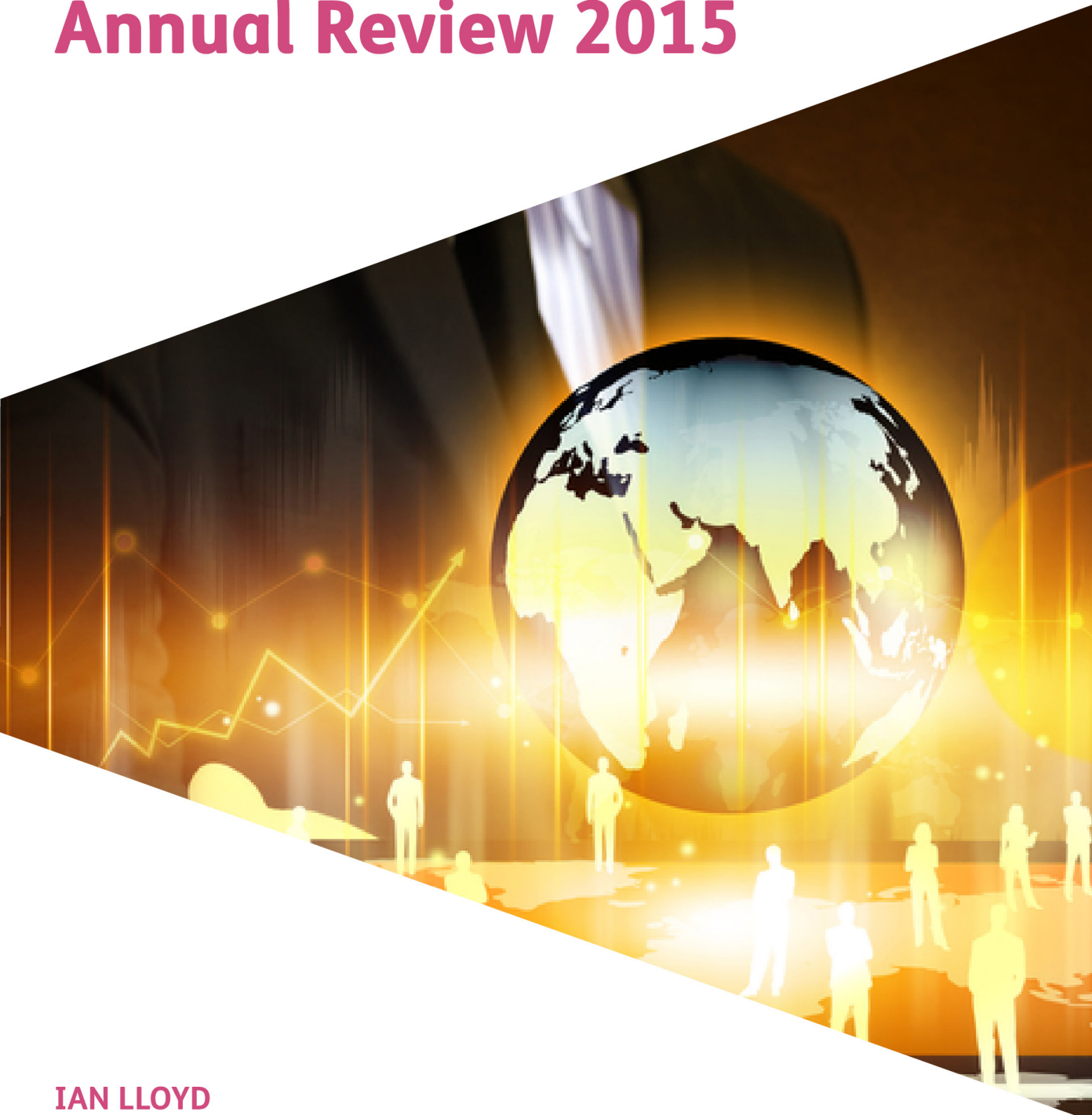


Citeline Pharma R&D Annual Review 2015



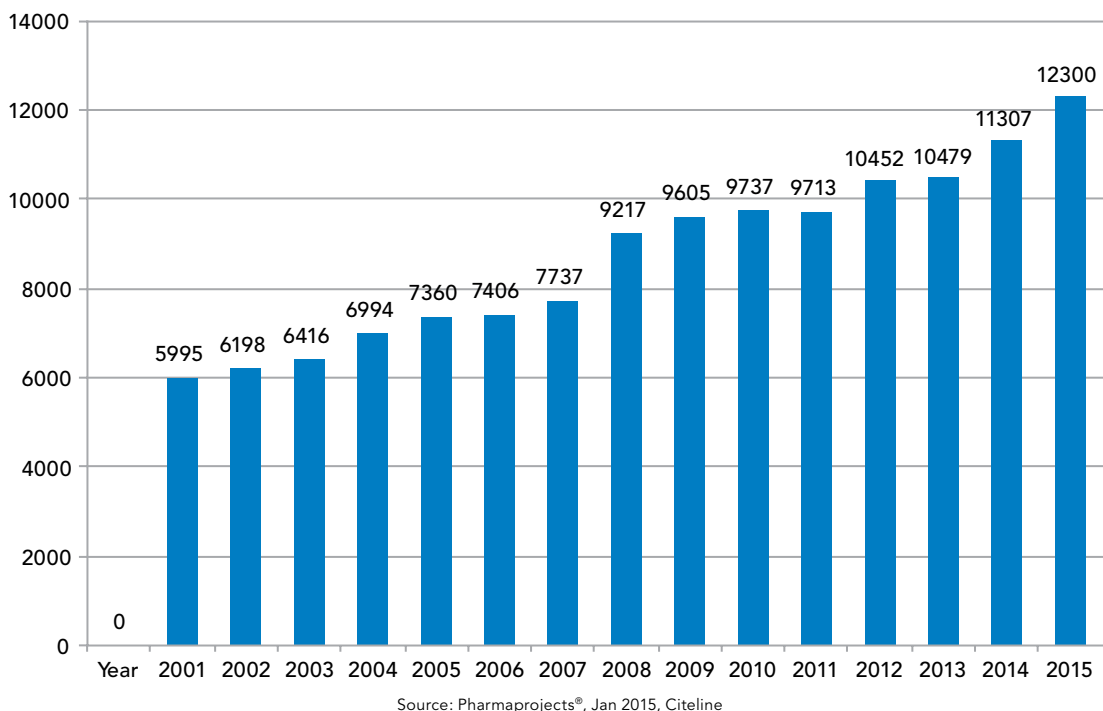
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Welcome to Citeline's 2015 review of trends in pharmaceutical R&D. For around a quarter of a century now, I've been taking an annual look at the state of the pharma R&D universe, and comparing it to similar data gathered over the many years during which Pharmaprojects has led the way in gathering global pharma R&D intelligence. By looking at our information on commercial pipelines over several years, I've identified new trends, raised alarm bells at worrisome signs, observed the brightest star drugs in the industry succeed, and watched some drug development strategies collapse into black holes. In this article, we will be seeing how the pipeline has changed in the past twelve months, and will be looking for pointers as to what the new year might bring. Here, we'll be concentrating on the pipeline as a whole. I'll be adding my thoughts as to the industry's success stories of the year just passed when we issue our review of 2014's New Active Substance launches as a supplement to this report, at the beginning of March 2015. This analysis, however, slices and dices pharma R&D as we report it in mid-January 2015.

Total pipeline size – a stellar expansion

As usual, we start with the keenly-anticipated headline figure, Citeline’s annual count of the total number of drugs in the development pipeline. This year, the news is again stellar: the figure’s up to 12,300. This is another sizeable year-on-year increase, a rise of 8.8%, exceeding even the 7.9% reported in 2014. In terms of actual numbers of R&D projects, at 993, considerably more have been added to the total through 2014 than the 828 extra from 2013. So it would seem that pipeline expansion is continuing and even gaining pace – along, presumably, with the inevitable concomitant increase in R&D expenditure.

Figure 1. Total R&D Pipeline Size by Year 2001–2015

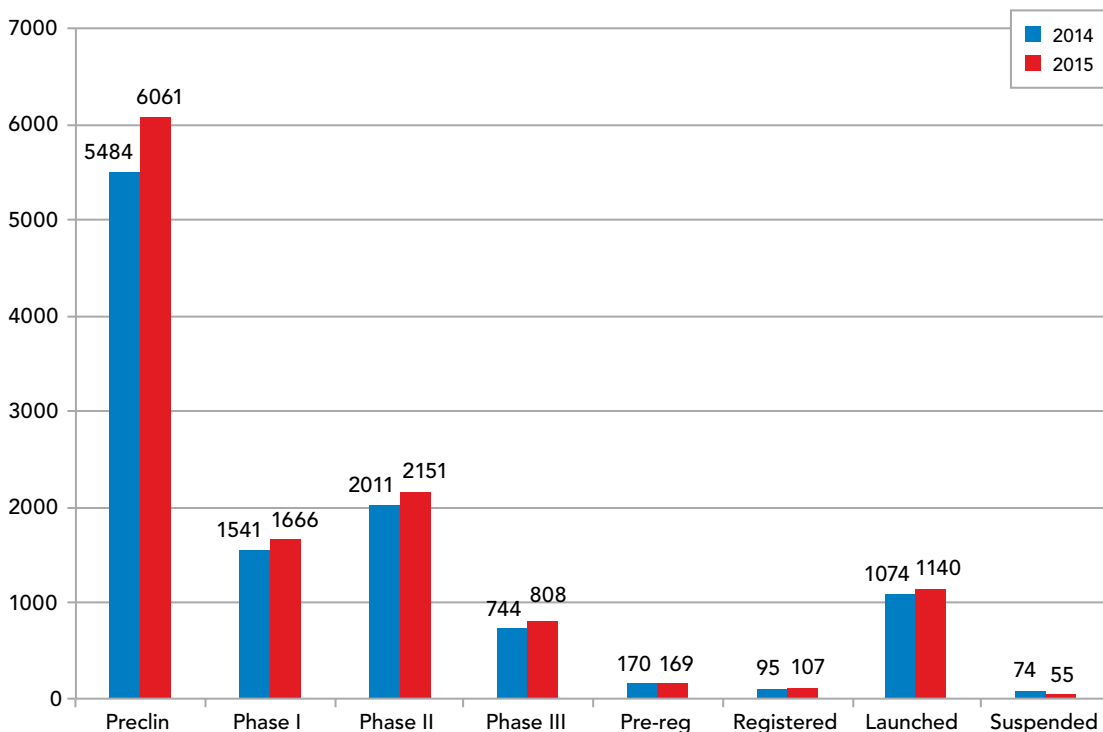


As Figure 1 shows, this number of 12,300 means that there are roughly twice as many drugs under development as there were just thirteen years ago. Does this mean we that we can expect a universe of 24,600 drugs in development in 2028? Highly doubtful – surely there will come a point where pipeline expansion slows as rising costs fail to keep up with returns. But, as this year’s big number shows, it doesn’t look like we are going to reach this point any time soon.

The 2015 pipeline by phase – clinical stages up, but preclinical leads the charge

Figure 2, breaking the pipeline out into the most advanced stage of development for each drug and comparing the data to that for last year, shows that increases in pipeline size occurred at almost all statuses. Particularly of interest are the rises at the clinical stages, but we'll look at these in more detail in a moment. Firstly, note that the number of preclinical drugs is up by 577, and thus accounts by itself for 58% of the increase in the number of active drugs we report. This is significant because this metric is the one which is most influenced by enhancements to our editorial practices and improved disclosure by pharma companies. Thus, this suggests that some, but crucially not all, of the growth in the total pipeline size may due to improved reporting. The increases seen at later development phases certainly do suggest, however, that there is some genuine expansion ongoing in the pharma pipeline universe.

Figure 2. Pipeline by Development Phase

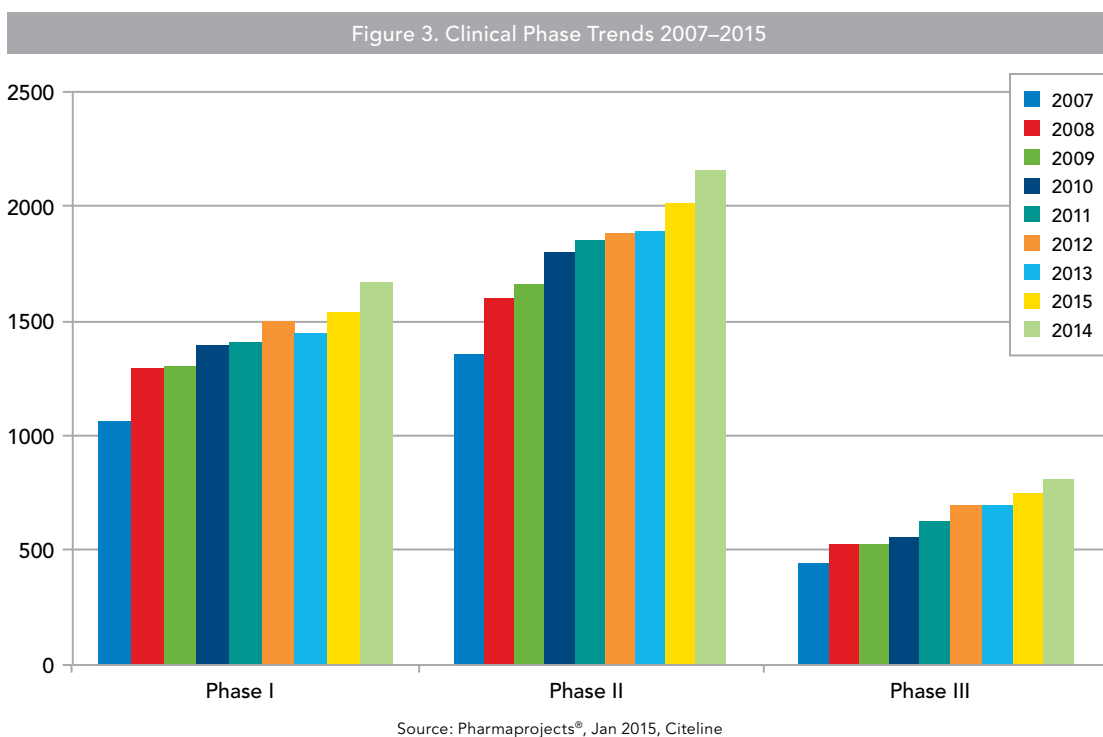


NB: A further 145 records for companion diagnostics in development complete the total pipeline figure; these records do not have a development phase.

Source: Pharamprojects®, Jan 2015, Citeline

The most keenly-tracked data from this graph is always the numbers of drugs which are in the three stages of clinical development. Our information here is always extremely robust, by dint of our collaboration with the leading worldwide source of clinical trials intelligence, Citeline's Trialtrove. Here we can see increases across the board; of 4.9% at Phase I, 7.0% at Phase II, and 8.6% at Phase III. Overall, the total number of drugs currently at any clinical phase has gone up by 7.7% to 4625. It's interesting to note that percentage figure, which is only just behind the overall pipeline expansion rate we saw at the top of this paper. This would suggest that there is significant growth in the pipeline not just across the board, but where it matters.

To give this further context, we can take a peek further back along the clinical trials time tunnel, and see how these growth rates compare to those seen in recent history. This is what Figure 3 visualizes. It's clear from this that the last couple of years have seen things gearing up a little following disappointing data during the 2011-2013 period. We can even surmise that, with the Phase III numbers increasing at a faster rate than those in Phase II, that there is some slight improvement in attrition rates at the end of the latter development stage.



It is worth commenting at this point, as we are often asked, on the reason for the seemingly counterintuitive fact that the Phase II figure always exceeds that for Phase I, when clearly drugs drop out of development between the two phases. This is an effect produced by the snapshot nature of the data: because drugs spend far less time passing through Phase I, at any one time, more are undergoing the much longer Phase II trials.

Top companies – steady state at the industry’s centre

Moving on to company pipelines, the Top 25 firms are very much the pharma industry’s supermassive black holes, these days often growing by drawing smaller bodies into their orbit and swallowing them up. But not a whole lot of sizeable merger and acquisition activity happened during 2014. The exception to this is Actavis, which absorbed Forest Laboratories mid-year and thus makes its debut in this year’s Table 1.

GlaxoSmithKline, despite having somewhat mixed fortunes during the year, retains the top spot with a portfolio of almost unchanged size. Just below it, the two Swiss superstars, Novartis and Roche, trade places, with the former taking this year’s second spot. Novartis actually has the most self-originated drugs of any company, although Lilly is the company whose pipeline has the highest proportion of homemade candidates.

Of course, the big story of the year was AstraZeneca’s thus far successful attempts to repel alien invaders from the planet Pfizer. So a wry smile will probably dance across the faces of those helming the UK company when they see that AZ’s pipeline size has this year overtaken that of its US aggressor. Its R&D pool of compounds has swollen by 12.7% to move it to fourth, whereas Pfizer slips down to seventh with a 2.9% decline. Of course, the US company is still financially the bigger beast, and while it may have lost the battles of 2014, who’s to say whether or not the war is over? AZ will no doubt face ongoing fierce scrutiny, and a couple of high-profile late-stage pipeline failures might well see it looking vulnerable to a renewed onslaught. For its part, Pfizer recently described its pipeline as ‘underappreciated’.

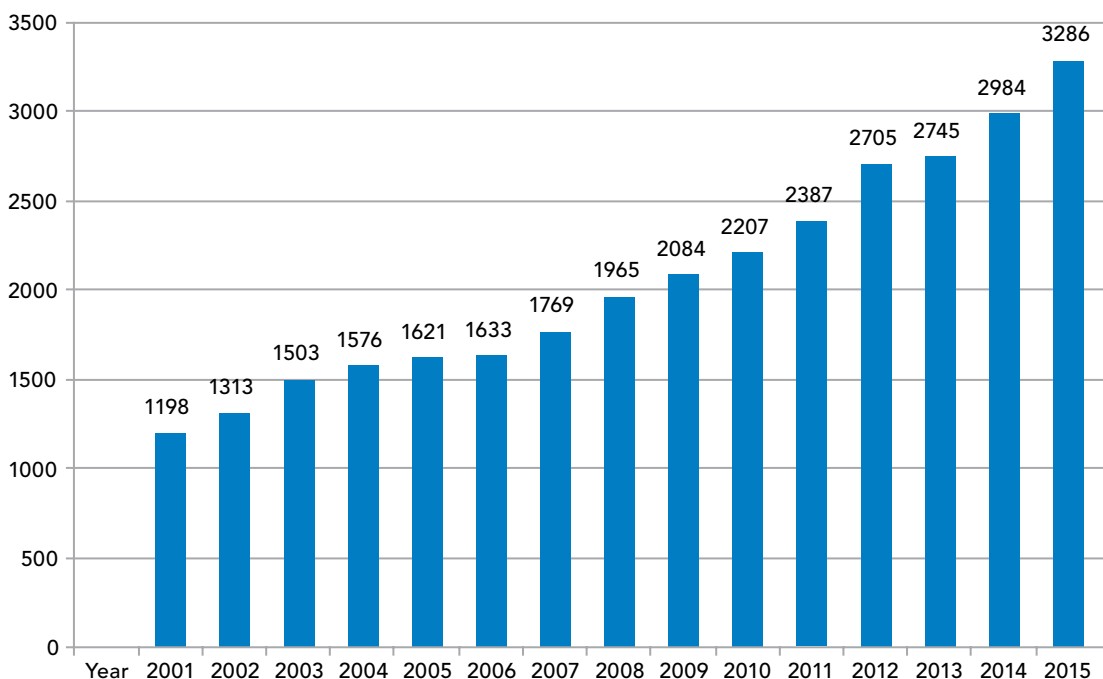
Table 1. Top 25 Pharma Companies by Size of Pipeline

POSITION 2015 (2014)	COMPANY	NO OF DRUGS IN PIPELINE 2015 (2014)	NO OF ORIGINATED DRUGS 2015
1 (1)	GlaxoSmithKline	258 (261)	163
2 (3)	Novartis	245 (223)	182
3 (2)	Roche	234 (248)	158
4 (5)	AstraZeneca	222 (197)	121
5 (8)	Johnson & Johnson	204 (164)	100
6 (6)	Merck & Co	199 (186)	130
7 (4)	Pfizer	199 (205)	132
8 (7)	Sanofi	184 (180)	84
9 (10)	Takeda	130 (132)	68
10 (11)	Eli Lilly	119 (124)	93
11 (9)	Bristol-Myers Squibb	118 (133)	88
12 (14)	Daiichi Sankyo	104 (96)	60
13 (16)	Bayer	99 (88)	68
14 (13)	Amgen	94 (97)	72
15 (17)	Teva	92 (84)	43
16 (12)	AbbVie	85 (113)	16
17 (-)	Actavis	84 (-)	34
18 (15)	Astellas	83 (92)	44
19 (19)	Eisai	82 (79)	47
20 (18)	Boehringer Ingelheim	82 (81)	56
21 (22)	Otsuka	81 (60)	48
22 (21)	Merck KGaA	67 (61)	31
23 (23)	Mitsubishi Tanabe Pharma	57 (56)	37
24 (20)	Dainippon Sumitomo Pharma	56 (63)	37
25 (-)	Kyowa Hakko Kirin	53 (-)	22

There isn't a whole lot else to report of note in the content of the Top 25, although AbbVie's drift downwards does stand out, as it further refines its strategy post-Abbott spin-out. In terms of where this set of giants sit in the pharma universe as a whole, the companies in the chart above originated 10.7% of the total number of active drugs. In a reverse of the trend seen in recent years, this is slightly up on the 10.5% seen last year, indicating a slight strengthening of big pharma's hegemony.

So, if for once the largest companies are taking a (very slightly) bigger slice of the pie, is there still also expansion at the other end of the spectrum, and what does this mean for the total number of companies currently involved in drug R&D? Figure 4, looking at the latter metric, also shows that plenty of new companies must be joining the fray.

Figure 4. Total Number of Companies With Active Pipelines 2001–2015



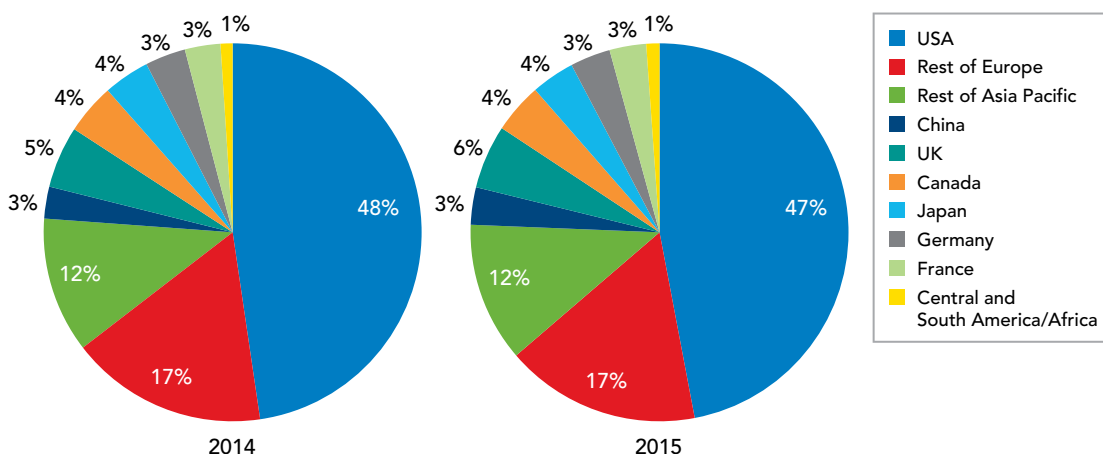
Source: Pharmaprojects®, Jan 2015, Citeline

The total number of companies with active pipeline drugs now stands at 3,286, up a huge 10.1% on the equivalent figure from January 2014. [Please note that the 2014 figure was incorrectly stated as 3,107 last year due to some subsidiaries being counted as companies]. This outstrips even the 8.7% expansion seen in the previous twelve months. Some of the extraordinary increase can be ascribed to our Analysts' continued efforts to uncover companies from ever more new sources, including this year, venturing into social media (such as LinkedIn) and university-based incubators, very much the 'nebulae' where new companies are born these days. As a result of this, through calendar 2014, a phenomenal 618 new companies performing drug R&D were identified and added to our database. The fact that the total number of companies only increased by about half this amount indicates that around 300 firms fell out of this data set during the year, due to inactivity, failure, or acquisition (although we only reported 79 cases of the latter). That is some rate of churn.

However, improved detection is probably only half the story. There are simply more and more companies starting to do drug R&D. This is borne out by looking at the growth in the number of very tiny companies, those with just one or two drugs in their portfolios. Last year, they accounted for 1,646 of the company total. This year, that's up to 1,844. So of the 3,286 R&D companies, 56% are really small. Plenty of bite-size collateral for big pharma to potentially gobble up there.

The distribution of company mass through the pharma universe this year however shows almost no change. As Figure 5 illustrates, the location of company headquarters amongst the major countries and regions is almost exactly the same as a year ago, with just the UK gaining a percentage point at the expense of the US. China continues to expand but the rate has slowed: 2015 reports 105 Chinese companies involved in original R&D, up from 85 the year before. It looked like China might replace South Korea as the second-biggest Asian country for novel drug development, but the Koreans had other ideas, keeping their noses ahead with 108 companies versus 95 in 2014.

Figure 5. Distribution of R&D Companies by HQ Country/Region 2014 and 2015

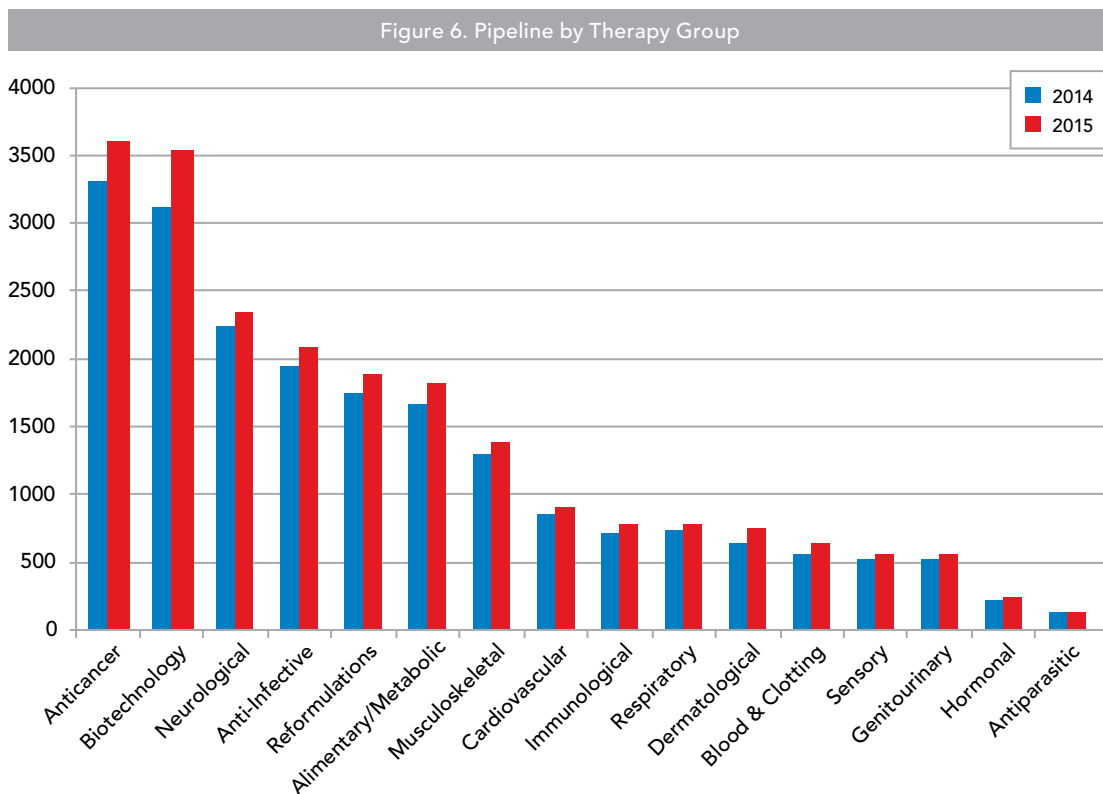


Source: Pharmaprojects®, Jan 2015, Citeline

The distribution of company mass through the pharma universe this year however shows almost no change.

Top therapy areas and diseases – cancer’s constellation of drugs brightens further

Let’s move our sights to observe what therapeutic areas and diseases are lighting up the sky this year. Much like twelve months ago, there are no therapeutic groups which have seen a decline in magnitude, but the rates by which they have risen do vary considerably.



Source: Pharamaprojects®, Jan 2015, Citeline

Firstly, cancer clearly remains at the centre of the therapeutic universe. The number of drugs with an oncological focus is up yet again this, the rise of 8.7% being very close to the average for the pipeline as a whole. Leaving aside the Biotechnology group of drugs (not strictly a therapeutic group), we can see that it has further extended its lead over its nearest rivals. This point will be reinforced as we drill down by therapeutic category and disease later in this section.

Neurological drugs again underperform, with the percentage increase for this area coming in at a paltry 4.5, the lowest for any of the therapeutic groups. The star performers are Dermatological and Sensory, which both post double-digit inflations (up 17.9% and 15.1%, respectively). Among the larger groups, Alimentary/Metabolic has the most impressive expansion, with a 9.5% growth in the number of pipeline projects. Note that throughout this section, there can be some double-counting if a drug is under development for more than one therapy or disease.

Table 2 sharpens the focus from the sixteen therapeutic groups to the 228 individual Therapeutic Categories we use to classify drugs. It shows not only the number of drugs for 2015 vs 2014, but also an indication of

the direction in which the numbers are moving. This highlights an interesting trend within cancer R&D at the top of the table: while the general cancer category remains virtually unchanged, immunological oncologicals rise sharply, indicating that such approaches are gaining in popularity within the cancer sphere. Elsewhere, we can see that drugs for GI inflammatory/bowel disorders contribute more to the increase seen in the Alimentary/Metabolic group than Antidiabetics do, and that Ophthalmological R&D is surging. The biggest drop is recorded by the general analgesic category, but this is entirely due to a new therapeutic category being created for Opioid analgesics and drugs being migrated there.

Table 2. Top 25 Therapeutic Categories

POSITION 2015 (2014)	THERAPY	NO OF R&D PRODUCTS 2015 (2014)	TREND
1 (1)	Anticancer, other	1835 (1834)	↔
2 (2)	Anticancer, immunological	1272 (989)	↑
3 (3)	Prophylactic vaccine, anti-infective	711 (644)	↑
4 (4)	Antidiabetic	547 (524)	↔
5 (8)	Ophthalmological, other	476 (398)	↑
6 (6)	Recombinant vaccine	470 (435)	↑
7 (7)	Anti-inflammatory	448 (427)	↔
8 (9)	Reformulation, fixed-dose combinations	439 (395)	↑
9 (13)	GI inflammatory/bowel disorders	397 (338)	↑
10 (16)	Monoclonal antibody, human	388 (321)	↑
11 (11)	Immunosuppressant	386 (361)	↔
12 (10)	Cognition enhancer	384 (382)	↔
13 (5)	Analgesic, other	384 (515)	↓
14 (14)	Antiviral, other	374 (337)	↑
15 (17)	Musculoskeletal	362 (314)	↑
16 (12)	Monoclonal antibody, other	356 (340)	↔
17 (20)	Biosimilar	350 (284)	↑
18 (15)	Cardiovascular	349 (334)	↔
19 (19)	Neurological	329 (311)	↔
20 (18)	Recombinant, other	327 (311)	↔
21 (21)	Monoclonal antibody, humanized	303 (280)	↔
22 (-)	Gene therapy	294 (-)	↑
23 (25)	Antiparkinsonian	288 (254)	↑
24 (-)	Anticancer, vaccine	275 (-)	↑
25 (23)	Neuroprotective	272 (264)	↔

Source: Pharmaprojects®, Jan 2015, Citeline

In the technology-related categories, recombinant vaccines increase, as do human monoclonal antibodies; for the latter, enough to put them into the Top 10 for the first time. There is a notable (and ongoing) uptick in biosimilar research, while gene therapy yoyos back into the Top 25 again, having been out in 2014, in 2013, and out in 2012.

Switching to an ever more powerful lens, we now examine the pipeline as categorized by the 1,258 individual diseases, or indications, which we report in Pharmaprojects as having been the focus of at least some drug development. Here, among other things, we can see clearly the individual cancer types currently enjoying

expanding R&D. Breast cancer cements its place at the summit, the number of drug candidates rocketing up 25%, and colorectal cancer is also up a remarkable 17.7% in the runner-up position. Also up – and up three places in the table too – non-small cell lung cancer posts a similarly notable 22.2% increase in candidate drugs. There are three other cancers in the Top 10 diseases, with prostate, ovarian and pancreatic cancer all recording rises of varying sizes. Further down Table 3, other cancer types on the march include non-Hodgkin’s lymphoma and acute myelogenous leukaemia, while this family of diseases also provides the only two entrants to this year’s Top 25, with head and neck cancer, and GI stomach cancer.

Table 3. Top 25 Indications			
POSITION 2015 (2014)	DISEASE*	NO. OF ACTIVE DRUGS 2015 (2014)	TREND
1 (1)	Cancer, breast	552 (440)	↑
2 (2)	Cancer, colorectal	413 (351)	↑
3 (6)	Cancer, lung, non-small cell	396 (324)	↑
4 (7)	Arthritis, rheumatoid	369 (322)	↑
5 (3)	Diabetes, Type 2	368 (346)	↑
6 (4)	Alzheimer’s disease	352 (340)	↔
7 (5)	Cancer, prostate	346 (336)	↔
8 (10)	Cancer, ovarian	342 (279)	↑
9 (8)	Cancer, pancreatic	339 (289)	↑
10 (9)	Pain, nociceptive, general	297 (287)	↔
11 (11)	Cancer, melanoma	276 (257)	↑
12 (12)	Asthma	263 (255)	↔
13 (13)	Cancer, brain	257 (212)	↑
14 (17)	Psoriasis	247 (182)	↑
15 (14)	Cancer, liver	220 (204)	↑
16 (15)	Parkinson’s disease	215 (196)	↑
17 (19)	Cancer, lymphoma, non-Hodgkin’s	203 (173)	↑
18 (22)	Cancer, leukaemia, acute myelogenous	196 (164)	↑
19 (–)	Cancer, head and neck	191 (–)	↑
20 (18)	Chronic obstructive pulmonary disease	189 (182)	↔
21 (24)	Cancer, myeloma	183 (162)	↑
22 (25)	Cancer, renal	177 (153)	↑
23 (20)	Infection, HIV/AIDS	173 (168)	↔
24 (–)	Cancer, gastrointestinal, stomach	169 (–)	↑
25 (16)	Infection, hepatitis-C virus	168 (188)	↓

*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®, Jan 2015, Citeline

But it’s not all about cancer. Also climbing the Top 10 is rheumatoid arthritis, up by 14.6%, while psoriasis shows where a tranche of the increases seen in the Dermatological therapy group came from. At the bottom of this chart, there’s an interesting fall for hepatitis-C therapeutics. The first launches of a new, but costly, generation of small molecule drugs has seen some companies, such as Vertex, Boehringer Ingelheim and Novartis, exit the area fearing that they will be unable to compete. This very much mirrors what was seen over a decade ago in HIV, which then tumbled down the table but in recent years has stabilized.

Types of pipeline drugs – the biological frontier edges forward

Moving to the differing types of drugs under development, Table 4 details the top 25 drug origins, dividing therapeutics into synthetic molecules, biologicals, and those naturally-derived, and segmenting these major classes further. Unsurprisingly, chemically-synthesized small molecules still account for the lion's share of molecules in the pipeline.

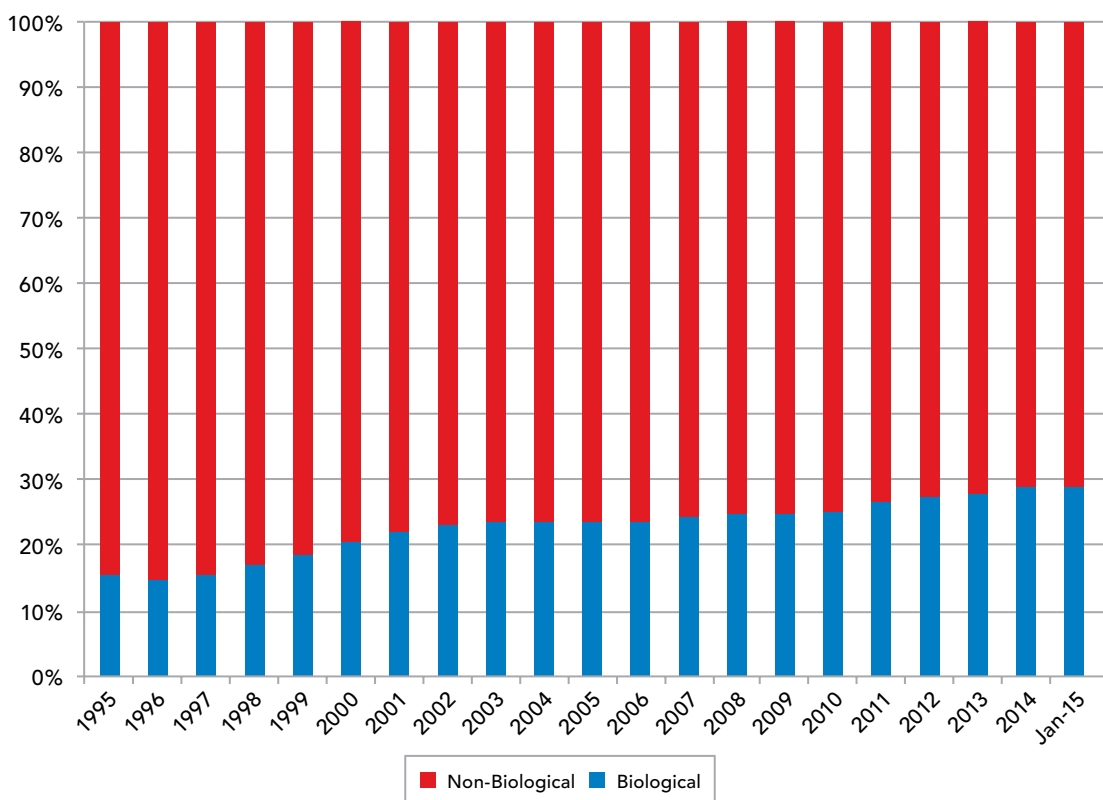
POSITION 2015 (2014)	ORIGIN	NO OF ACTIVE DRUGS 2015 (2014)	TREND
1 (1)	Chemical, synthetic	6771 (6262)	↑
2 (2)	Biological, protein, antibody	1267 (1163)	↑
3 (3)	Biological, protein, recombinant	887 (808)	↑
4 (4)	Biological, protein	408 (367)	↑
5 (5)	Chemical, synthetic, peptide	399 (346)	↑
6 (6)	Biological, virus particles	303 (303)	↔
7 (7)	Chemical, synthetic, nucleic acid	291 (285)	↔
8 (8)	Biological, nucleic acid, viral vector	268 (228)	↑
9 (11)	Biological, cellular, autologous	170 (122)	↑
10 (9)	Natural product, plant	166 (151)	↔
11 (10)	Biological, peptide	165 (136)	↑
12 (12)	Biological, nucleic acid, non-viral vector	122 (118)	↔
13 (15)	Biological, cellular, heterologous	111 (99)	↑
14 (13)	Biological	103 (113)	↓
15 (18)	Biological, cellular	100 (64)	↑
16 (14)	Biological, peptide, recombinant	98 (112)	↓
17 (16)	Biological, bacterial cells	94 (94)	↔
18 (17)	Chemical, semisynthetic	79 (76)	↔
19 (19)	Biological, nucleic acid	70 (48)	↑
20 (22)	Natural product	42 (37)	↑
21 (20)	Natural product, bacterial	41 (44)	↔
22 (23)	Biological, other	40 (27)	↑
23 (21)	Chemical, synthetic, isomeric	37 (43)	↓
24 (24)	Natural product, animal	30 (26)	↔
25 (25)	Natural product, fungal	21 (22)	↔

Source: Pharmaprojects®, Jan 2015, Citeline

A number of biological drug types go up, notably a couple covering cell therapies. But what of the broader trend, seen in Figure 6, Table 2, and here, of increases in biologicals? Are, as is popularly believed, biologicals gradually replacing small molecules at the heart of drug RD efforts? To answer this question more conclusively, we should examine Pharmaprojects' unique Trends data to see if the biologicals really look like they're staging a takeover.

It would appear from Figure 7 that if they are, they are doing so by stealth. The graph shows the proportion of the pipeline made up of biologicals versus non-biologicals right back to 1995. This clearly shows that, although biologicals gained territory through the late nineties, for much of the subsequent decade, the proportion was pretty stable. Only since 2010 have biologicals been inching forward again, but it is a very slow advance. Currently they account for 29.1% of drug candidates, up very modestly from 28.9% last year. But, taken over the entire twenty year period, their slice of the R&D action has almost doubled.

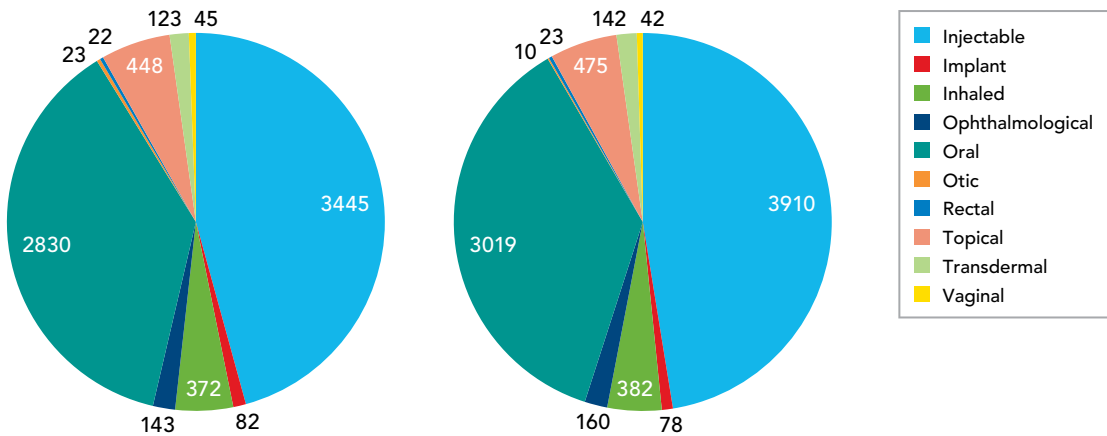
Figure 7. Biologicals Vs. Small Molecules as a Percentage of the Pipeline 1995–2015



Source: Pharmaprojects®, Jan 2015, Citeline

Is this change in the make-up of the kinds of drugs under development being reflected in concomitant changes in delivery methods? The most recent figures do suggest that this is the case (see Figure 8). 2015 does indeed have a slightly higher proportion of injectables than 2014 did (47.4% vs 45.7%), whereas the equivalent data for oral drugs shows a small decline (36.6% vs 37.6%). It seems that the price of less convenient delivery is one which the industry – and the patient – is prepared to pay for the efficacy and superior targeting which many biological drugs bring to the table.

Figure 8. Pipeline by Delivery Route 2014 & 2015



Source: Pharmaprojects®, Jan 2015, Citeline

It seems that the price of less convenient delivery is one which the industry – and the patient – is prepared to pay for the efficacy and superior targeting which many biological drugs bring to the table.

Mechanisms and Targets – immunological mechanisms and growth factor targets prosper

In our final two tables, we turn to how drugs are working and the protein targets they are hitting to bring about their activity. In Table 5, which looks at drugs by their pharmacological action, immunological strategies fare well, with increases or debuts for T cell inhibitor, T cell stimulant, and the newly-created Desensitizer class.

Table 5. Top 25 Mechanisms of Action (Pharmacologies)

POSITION 2015 (2014)	MECHANISM OF ACTION (PHARMACOLOGY)	NO. OF ACTIVE COMPOUNDS 2015 (2014)	% OF COMPOUNDS PR/R/L
1 (1)	Immunostimulant	1593 (1441)	7.7
2 (2)	Immunosuppressant	217 (185)	28.6
3 (3)	Angiogenesis inhibitor	177 (169)	15.8
4 (4)	Opioid mu receptor agonist	134 (132)	30.6
5 (5)	Apoptosis stimulant	128 (119)	11.7
6 (7)	Tumour necrosis factor alpha antagonist	111 (94)	18.0
7 (10)	Cyclooxygenase 2 inhibitor	103 (81)	42.7
8 (6)	DNA inhibitor	100 (110)	20.0
9 (11)	Vascular endothelial growth factor (VEGF) receptor antagonist	97 (77)	14.4
10 (8)	Glucocorticoid agonist	91 (93)	35.2
11 (13)	Cyclooxygenase 1 inhibitor	79 (64)	48.1
12 (12)	DNA topoisomerase II inhibitor	74 (72)	27.0
13 (15)	DNA synthesis inhibitor	66 (62)	27.3
14 (20)	T cell inhibitor	64 (56)	20.3
15 (17)	Gene expression inhibitor	64 (60)	0.0
16 (22)	Insulin secretagogue	62 (55)	41.9
17 (14)	Tubulin inhibitor	62 (64)	11.3
18 (-)	Desensitizer	61 (-)	32.8
19 (21)	Glucagon-like peptide 1 agonist	61 (56)	11.5
20 (17)	Opioid delta receptor agonist	60 (62)	31.7
21 (-)	T cell stimulant	59 (-)	6.8
22 (-)	Angiotensin II 1 antagonist	56 (-)	33.9
23 (19)	Opioid kappa receptor agonist	55 (59)	32.7
24 (25)	Progesterone receptor agonist	55 (54)	40.0
25 (24)	Cell wall synthesis inhibitor	54 (54)	40.7

Source: Pharmaprojects®, Jan 2015, Citeline

In Table 6, which looks at the Top 25 proteins which drugs are targeted against to achieve their activity, another trend emerges: increasing work on growth factors and their receptors. The epidermal growth factor receptor is a high climber within the Top 10, which also sees the related Her-2 on the rise. Further down the chart, vascular endothelial growth factor A posts the biggest upwards move. But pole position is unchanged, with the opioid pain target mu1 remaining the single most popular target for drug development in 2015.

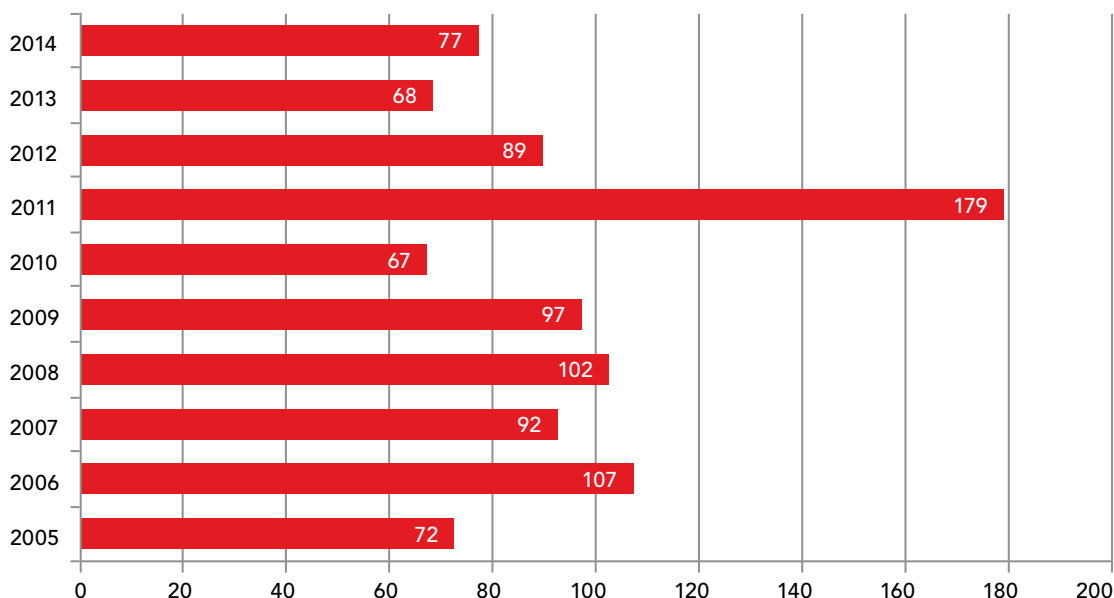
Table 6. Top 25 Drug Protein Targets

POSITION 2015 (2014)	TARGET	NO. OF ACTIVE COMPOUNDS 2015 (2014)
1 (1)	opioid receptor, mu 1	156 (155)
2 (2)	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	122 (121)
3 (6)	prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) [COX-2]	107 (85)
4 (3)	tumour necrosis factor	106 (91)
5 (10)	epidermal growth factor receptor	89 (77)
6 (4)	opioid receptor, kappa 1	85 (87)
7 (9)	<i>erb-b2 receptor tyrosine kinase 2</i>	85 (79)
8 (7)	insulin receptor	84 (82)
9 (8)	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) [COX-1]	82 (81)
10 (5)	polyprotein, hepatitis-C virus	81 (86)
11 (23)	vascular endothelial growth factor A	72 (52)
12 (12)	gag-pol, HIV-1	71 (65)
13 (14)	adrenoceptor beta 2, surface	71 (65)
14 (11)	opioid receptor, delta 1	65 (67)
15 (13)	dopamine receptor D2	63 (65)
16 (16)	estrogen receptor 1	62 (59)
17 (20)	glucagon-like peptide 1 receptor	62 (56)
18 (15)	progesterone receptor	58 (62)
19 (24)	membrane-spanning 4-domains, subfamily A, member 1	57 (50)
20 (-)	angiotensin II receptor, type 1	57 (-)
21 (17)	mechanistic target of rapamycin (serine/threonine kinase) [mTOR]	54 (58)
22 (21)	amyloid beta (A4) precursor protein	53 (55)
23 (18)	<i>kinase insert domain receptor</i>	52 (57)
24 (19)	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [PI3K]	52 (57)
25 (22)	tubulin, beta class I	52 (53)

Source: Pharmaprojects®, Jan 2015, Citeline

By January 2015, 2,627 individual proteins had at some point been reported or determined by us to have been targeted by drugs in development since our database began in 1980, of which 2,575 remain so. This will give us our 'innovation index' – the number of new targets for which drug development was first reported during the year, and across calendar 2014, this stands at 77. Figure 9 put this into context.

Figure 9. Number of New Drug Protein Targets Identified by Pharmaprojects by Year.



Source: Pharmaprojects®, Jan 2015, Citeline

This figure has tended to ping around rather a lot, and is to some extent influenced by external factors, such as curation of the NCBI's Gene database from which targets are added, but the take home here is really the fact that the overall level of target addition is not really increasing. This year's number was 77 – slightly better than 2013, slightly worse than 2012. Innovation continues, but at a somewhat pedestrian rate; there is certainly no sign of a scientific big bang suggesting drug development innovation is in an expansionary phase. But the galaxy of drug targets does continue to slowly expand.

An ever-expanding universe?

The year 2014 saw the 50th anniversary of the discovery and confirmation of cosmic microwave background radiation, a finding which enshrined the Big Bang Theory as the prevailing doctrine describing the origin and evolution of the cosmos. Although opinions differ and theories still compete, most cosmologists believe that, rather than reaching a point when it begins to contract again, expansion of the universe will continue forever, but that the rate will slow and the universe will gradually dim and die from 'heat death'. Is this a chilling parable for our own pharma R&D universe? The expansion in the pipeline continues every year, showing no sign of slowing or reversing, but could this at the same time see the pharmaceutical industry gradually running out energy, or indeed, funds? It certainly needs to birth an increasing number of new star compounds to fuel this ongoing growth. But even if it does, as companies face commercial and pricing pressures as never before, can its R&D universe expand forever?

Once again, it's pretty much good news across the board in terms of the metrics covered in this report. And early signs indicate that 2014 was a stellar year for new drug approvals. At the time of writing, our definitive list of New Active Substance (NAS) launches for 2014 is still being finalized, but it is already looking like being a record-breaking year. I'll return to this subject in early March, with Citeline's New Active Substances supplement to this report. Keen observers of the industry should train their telescopes on that, and continue to watch the skies via Pharmaprojects as the story of 2015 unfolds. Pharma R&D will, like space exploration, continue to be a high-risk venture, but when it is successful, the rewards can be truly astronomical.

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