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Citeline Pharma R&D Annual Review 2014

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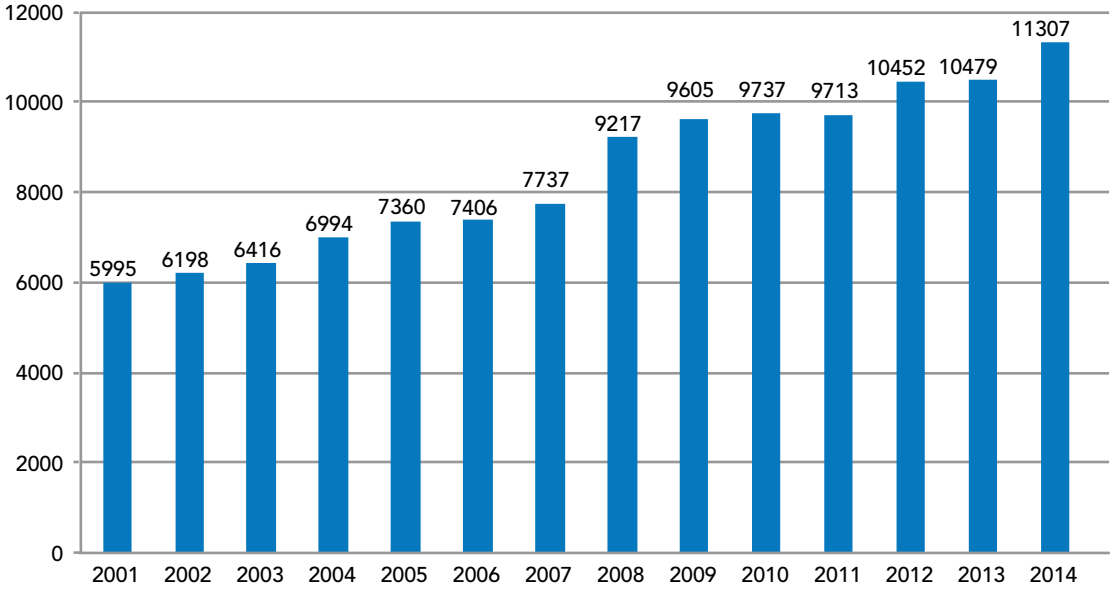
Welcome to Citeline's 2014 review of trends in pharmaceutical R&D. For over twenty years, I've been taking an annual look at the state of the pharma nation, freezing the pipeline in time and comparing it to similar data points in previous years. By looking at our information on commercial drug R&D over several years, I've identified new trends, raised alarm bells at worrisome signs, or banged the drum for the industry's successes. In this article, we will be seeing how the pipeline at the very start of 2014 has changed in the past twelve months, and 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 2013's New Active Substance launches as a supplement to this report, at the beginning of March 2014.

Total size of pipeline – up, up and away!

So let's dive straight in with the always hotly-anticipated 'headline figure' for the year – the total size of the global pipeline. Citeline's drug information service, Pharmaprojects/Pipeline, here counts a pipeline drug as a single entity or project which is somewhere on its journey from preclinical development through to market launch. It does also include drugs which are already commercially available but are continuing in development for follow-on indications or for additional markets. And this year, the news is striking. With 11,307 drugs currently in R&D, the pipeline has swollen by a whopping 7.9%.

Figure 1. Total R&D Pipeline Size by Year 2001-2014



Source: Pharmaprojects® Pipeline®, January 2014

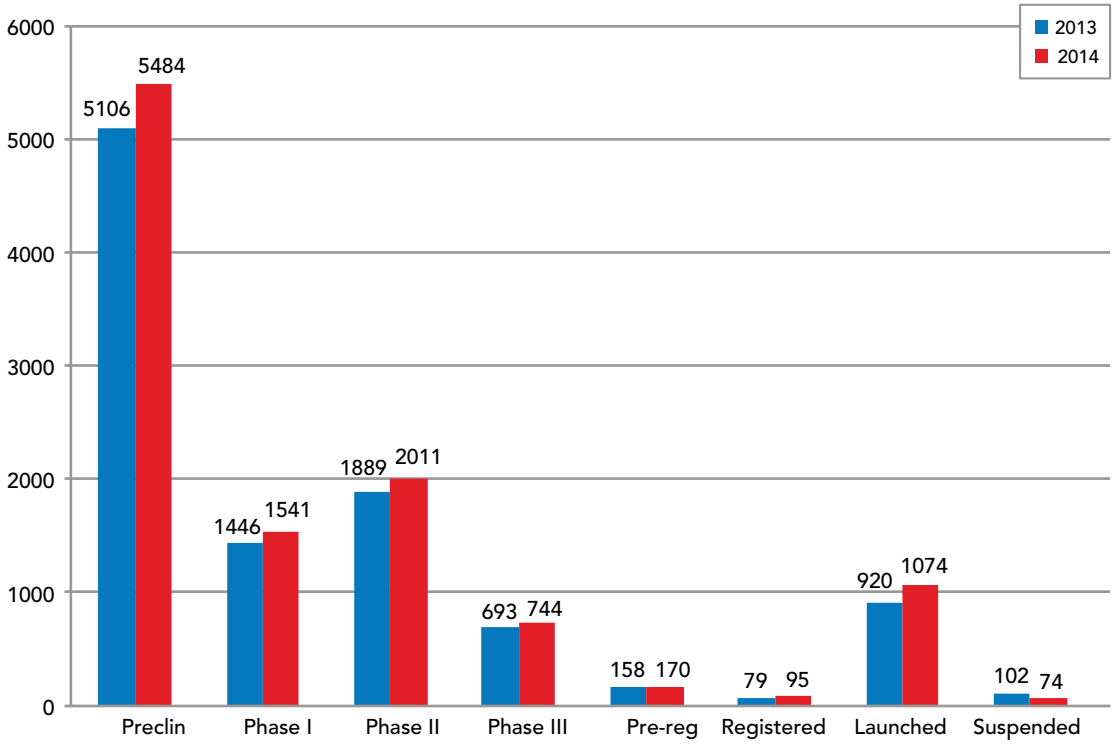
A look at Figure 1, which shows the equivalent figure for every year going back to 2001, highlights why this percentage increase is remarkable in more than one way. Firstly, leaving aside the anomalous increase seen in from 2007 to 2008 where the rise is hugely flattered by the merging of drug data from our original database with that from the then newly-acquired Citeline database of clinical trials (Trialtrove), this is by

some distance the biggest annual increase in numbers ever seen. It's also the heftiest in percentage terms in a decade, since the 9.0% seen from 2003 to 2004. This however only represented a jump of 578 drugs – this year's rise was of almost one and a half times as many. But the expansion is also in sharp contrast to the change seen last year, which was almost flat. In fact, it seems that the curious 'step-wise' progression of pipeline growth is undergoing another cycle. There are no internal changes in editorial procedure this year which can explain this sudden upwards trajectory, so we are forced to conclude that there is genuine growth in the industry's pipeline, perhaps tinged with greater disclosure from the pharmaceutical companies. If the latter is a big factor here, we would expect bigger increases at the earlier stages of development where publication of compound data is more discretionary, so let's move to break the pipeline down by development stage.

The 2014 pipeline by phase – increases across the board

The first thing to note when we examine Figure 2, which looks at the numbers of drugs at each global development status both now and a year ago, is that there are more drugs at every active development status now. But this pattern of increase is indeed not uniform. While the number of drugs at Phase I and Phase II clinical trials has increased by 6.6 and 6.5%, respectively, those at the Preclinical stage of development have grown their number by 7.4%. This would indicate that a small part of the pipeline size growth could have come from increased disclosure, or better detection on our part, but that the majority of the increase is likely genuine organic growth. Indeed, the Phase III figure rose by the same percentage as the Preclinical one. Interestingly, the biggest growth is seen with the Launched (but still Active) drugs – up 16.7%. This is surely evidence of companies increasingly wringing more from their successful drugs by continuing to develop them post-marketing for additional indications.

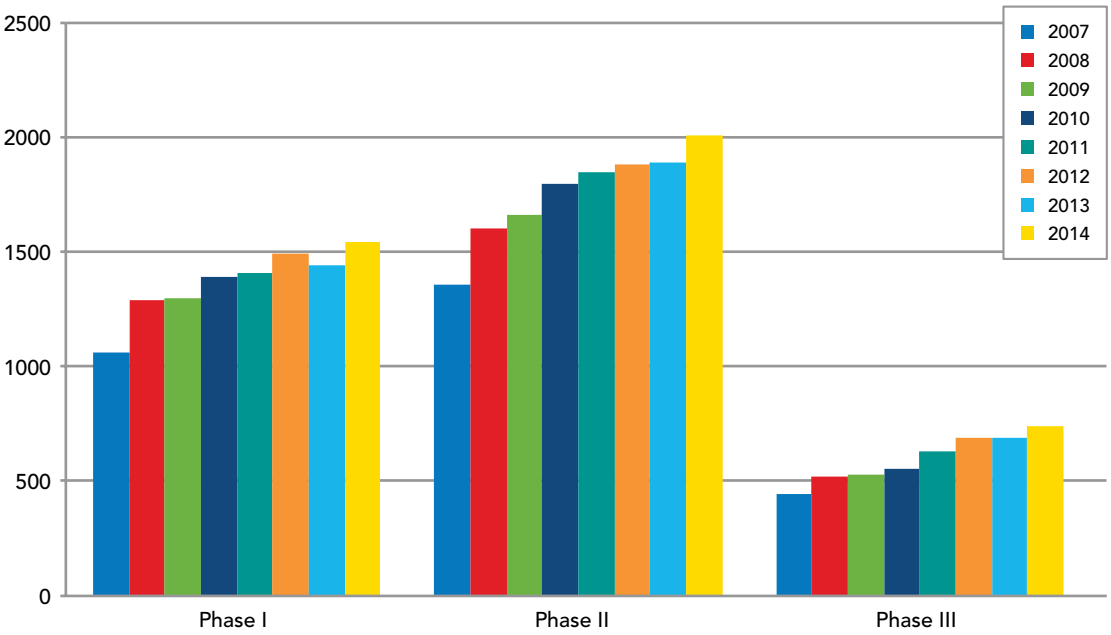
Figure 2. Pipeline By Development Phase



Source: Pharmaprojects® Pipeline®, January 2014

The statistics which are usually of most interest here are those surrounding the clinical phases of development, in many ways the 'beating heart' of the pipeline. It's here that the most clues as to the overall health of the industry in the coming years can be garnered, so it's worthwhile taking a slightly longer term look at the data here. In Figure 3, we look back to 2007 to see how the numbers of drugs at Phases I to III have changed over an eight year period.

Figure 3. Clinical Phase Trends 2007-2014



Source: Pharmaprojects® Pipeline®, January 2014

Regular readers of the Citeline Pharma R&D Annual Reviews may recall that last year, alarm bells were sounding at the Phase I figure, which had shown a decline for the first time ever. Happily, this appears to have been something of a blip, with the 2014 number more than recovering. Similarly, after flattish data at Phase II and Phase III in 2013, this year sees a resumption of growth, with the data for Phase II looking particularly impressive. The numbers of drugs in Phase I, II and III have in fact grown by a formidable 45.3, 47.9 and 66.9%, respectively, over the study period, and eight years is really not that long a time. This is all mightily encouraging.

As always, a quick note about the seemingly counterintuitive fact that the Phase II figure always exceeds that for Phase I figure, 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 – stability rules

So if it's all good news at the top end of our analysis, who are the movers and shakers which stand to benefit from – or are producing – this upward surge in the industry's thermometer? Table 1 gives the standings of the Top 25 pharma companies by the size of their pipelines. This shows GlaxoSmithKline (GSK) maintaining its place at the summit, but with a much-reduced lead over its nearest rival, Hoffmann-La Roche. The latter Swiss-based multinational is also revealed to be the company which originated the most of its development compounds. Interestingly, GSK is the only one of the top five to have fewer R&D projects this year than last, albeit by only eight drugs. The biggest mover is AstraZeneca (AZ), up to number five on the back of a 25% expansion in its portfolio. The company did acquire a number of small companies during 2013, including AlphaCore, Pearl Therapeutics and Aplimmune, but this alone would not account for such an increase.

Table 1: Top 25 Pharma companies by size of pipeline

POSITION 2014 (2013)	COMPANY	NO OF DRUGS IN PIPELINE 2014 (2013)	NO OF ORIGINATED DRUGS 2013
1 (1)	GlaxoSmithKline	261 (269)	152
2 (2)	Hoffmann-La Roche	248 (227)	179
3 (3)	Novartis	223 (215)	158
4 (5)	Pfizer	205 (202)	136
5 (8)	AstraZeneca	197 (157)	110
6 (4)	Merck & Co	186 (207)	115
7 (6)	Sanofi	180 (183)	83
8 (7)	Johnson & Johnson	164 (157)	81
9 (9)	Bristol-Myers Squibb	133 (141)	104
10 (10)	Takeda	132 (141)	71
11 (11)	Eli Lilly	124 (117)	103
12 (12)	AbbVie*	113 (114)	3
13 (13)	Amgen	97 (95)	75
14 (15)	Daiichi Sankyo	96 (91)	54
15 (14)	Astellas	92 (93)	54
16 (16)	Bayer	88 (87)	57
17 (18)	Teva	84 (75)	36
18 (19)	Boehringer Ingelheim	81 (68)	57
19 (17)	Eisai	79 (81)	45
20 (21)	Dainippon Sumitomo Pharma	63 (54)	43
21 (20)	Merck KGaA	61 (56)	24
22 (-)	Otsuka	60 (-)	37
23 (-)	Mitsubishi Tanabe Pharma	56 (-)	35
24 (25)	Celgene	53 (47)	26
25 (23)	Shionogi	52 (49)	25

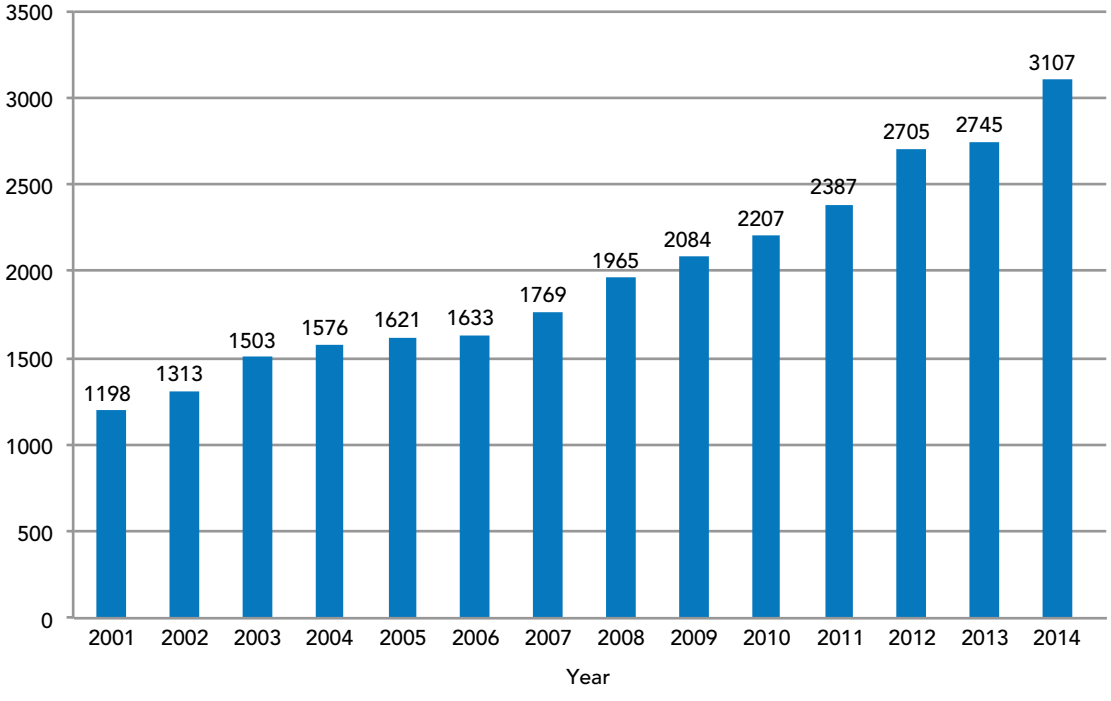
*In 2013, Abbott was at No.12 as data was taken just prior to the AbbVie spin-off. The reason that AbbVie has so few originated compounds is that Abbott remains as a discontinued originator on the compounds which it spun-out to AbbVie (which is listed as a licensee)

Source: Pharmaprojects® Pipeline®, January 2014

Elsewhere, what's most remarkable is how little has changed. In what was a year of relative stability for big pharma in terms of mergers and acquisitions – or a lack thereof – most companies simply shuffled around slightly in our chart. Despite the continuing lull in mega-merger activity, we still reported on 64 mergers or acquisitions over the course of the year, which is more than one a week on average. But it's the complexion of this activity which has changed, with big pharma firms increasingly, as AZ did, picking up tiny companies in order to get their hands on a specific technology or drug. This is a prime way in which larger concerns are seeking to broaden their portfolios at a lower cost, and with far less disruption, than via the traditional mega-merger. It might also be viewed as an indictment of their own inability to innovate, and proof that small companies are the ones with the intellectual agility needed to perform truly creative R&D.

So if the big pharma sharks are busy gobbling up the smaller fish, how has this affected the overall population profile of the R&D ocean? Well, certainly there are more than enough new companies diving into R&D to replenish this loss. In fact, as Figure 4 shows, 2013 saw the biggest upsurge in the total number of companies with pipelines seen to date. As of Jan 2014, there were 3,107 pharma R&D firms, an increase of 362 (13.2%) on the figure from twelve months ago. So perhaps this is the real story this year – an increase in pipeline size which is to some extent being fuelled by a surge in new company creation.

Figure 4. Total Number of Companies with Active Pipelines 2001-2013



Source: Pharmaprojects® Pipeline®, January 2014

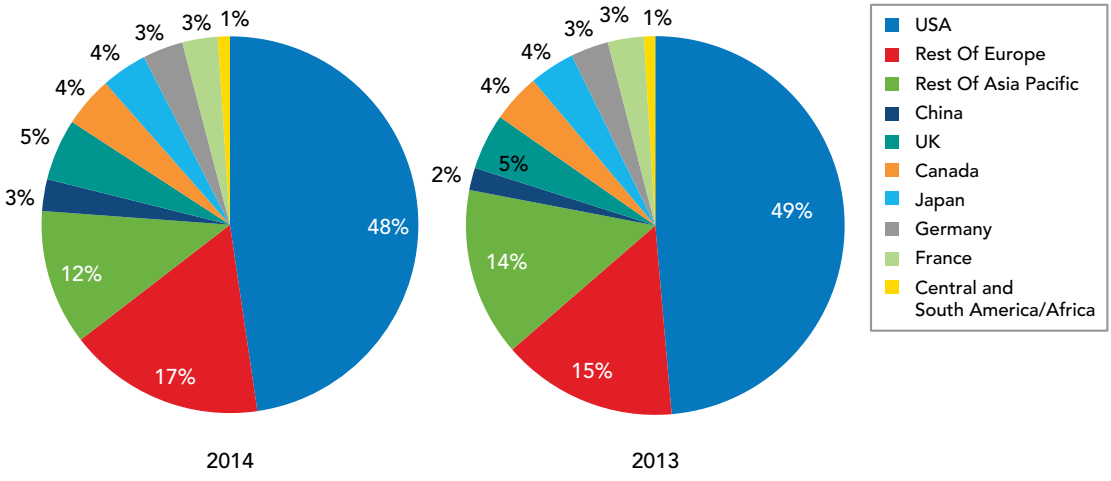
We can look into this apparent proliferation of R&D minnows in a bit more detail. Last year, 1,475 of the 2,705 reported companies had just one or two candidates in their pipelines. The equivalent figure this year is up to 1,646. So it seems that the growth in the number of tiny firms is actually only part of the story. Interestingly, the rate of company addition to our data set, with 492 being newly identified over the past twelve months, is only marginally above that seen in the previous year, but then the total number was almost flat. This would lead us to believe that fewer companies left the R&D space in 2013 than in 2012, which is surely a positive sign, since many of those which drop off the radar do so as a result of business failure. It also means that, as much as the big pharma fish are feeding on their smaller niche cousins, there

is an ever richer shoal of new companies to harvest. This enrichment of pharma's biosphere, perhaps more than anything else, gives us cause for great optimism for the future of the industry.

It also forms part of a trend we have been observing over a number of years now where, as the smaller companies multiply, the power of the biggest pharma companies is beginning to dwindle somewhat. This year, the Top 10 multinational firms in Table 1 have originated just 10.5% of all compounds in R&D, down from 11.5% last year and 13.4% the year before. This is not surprising when you consider that certain of the Top 10 actually have smaller pipelines this year than last. But is this an intrinsically bad thing? Many would argue that it's quality rather than quantity that these companies need, and that an organization can only sensibly manage a portfolio of a limited size. The proof of the pudding, as ever, can only be in seen in the industry's ultimate successful output of new drugs onto the market. It's this topic which we'll be analyzing in detail in the New Active Substances in 2013 supplement to this report, to be published in March 2014.

The geographical distribution of the industry is also changing, albeit extremely gradually. Figure 5 looks at the headquarter countries of the companies developing drugs and contrasts it with the same data from a year ago. It shows a further small decline in US dominance: America had 50% of companies in 2012, and has lost 1% share in both years since then.

Figure 5. Distribution of R&D Companies by HQ Country/Region 2013 and 2014



Source: Pharmaprojects® Pipeline®, January 2014

But the shift is very subtle. Europe is holding firm, accounting for 29% of companies, as last year. There is little evidence again of growth in emerging markets this year, with the APAC region's share actually down just a little from 18 to 17%.

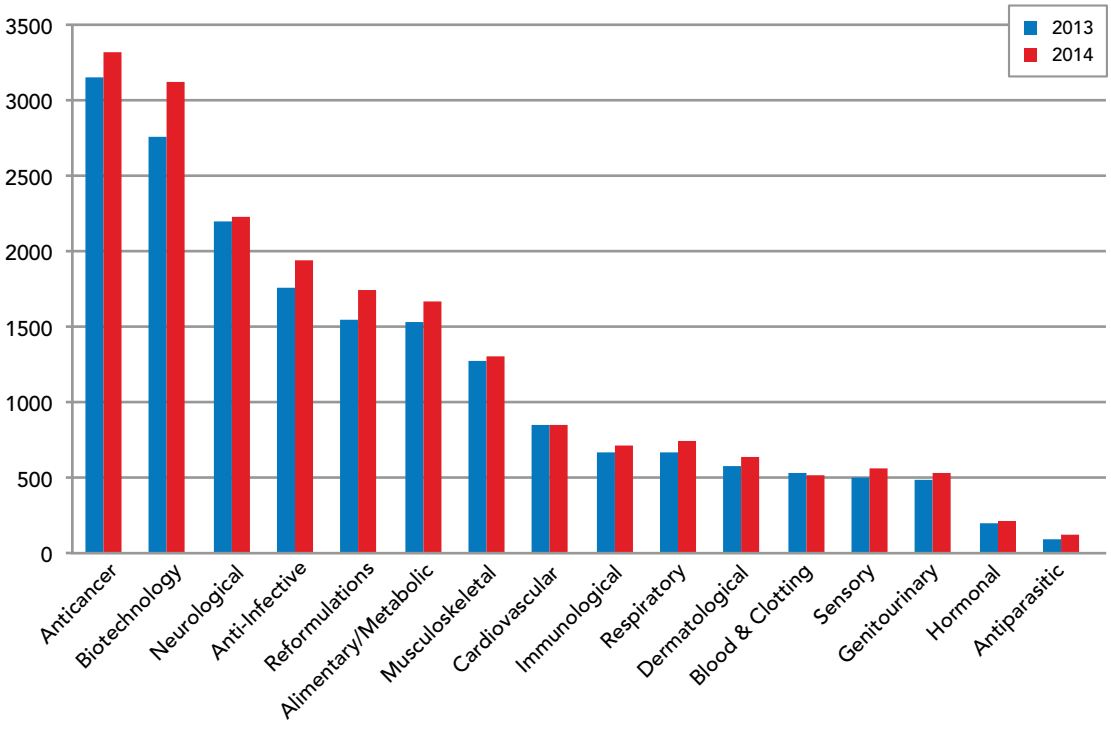
But these figures hide one definitive trend – the growth of China. It is now the eighth biggest territory in terms of number of companies producing R&D compounds, up from thirteenth, and with the actual number of companies far surpassing 2012's growth rate of 9% to hit 44% through 2013. With 85 companies, China is fast closing on S Korea to be the second largest Asian pipeline provider, after which it will no doubt have the R&D powerhouse of Japan in its sights. But Japan will not surrender its pole position without a fight, and it's notable that the only two companies this year to enter the Top 25 – Otsuka and Mitsubishi Tanabe Pharma – are both Japanese.

Top therapy areas and diseases – growth variations found across therapeutic groups

So having dissected the industry by who's who, it's time to move to what's what in the pipeline. With such a big increase in drug R&D across all phases, it's interesting to note that there are considerable variations this year when you carve up the pipeline by the major therapeutic groups. This is shown in Figure 6, which contrasts the 2014 and 2013 figures for each of the fourteen major therapeutic areas and the reformulation, biotechnology groupings. Note that in this figure, a drug may be counted more than once if it has multiple therapeutic activities.

Firstly you will see that there is growth across all areas, with the notable exception of the presently moribund Blood & Clotting drugs area, and the related area of Cardiovascular has grown only very slightly. But within the other areas, there are considerable variations in growth rates. Top of the pack as ever, Anticancer drugs increase by 4.9%, for once not outperforming the global growth rate (remember, that stands at 7.9%). However, this lower than average expansion still puts the oncology set further ahead than last year of its nearest rival, Neurological, which only experienced a paltry growth rate of 1.6%.

Figure 6. Pipeline by Therapy Group



Source: Pharmaprojects® Pipeline®, January 2014

The star performers this year are Anti-infectives, whose pipeline swelled by 10.2% after a flat 2012-2013, and Alimentary/Metabolic, up by 8.8%. The latter actually experienced a decline last year, so this is a considerable reversal of fortune. Actually, purely in percentage terms, the Antiparasitic and Hormonal groups experienced the largest growth rates, but as can be seen, they are the two smallest players so this is an increase in a goldfish bowl as opposed to the ocean. Three other therapeutic groups also outperformed the global growth rate: Respiratory (9.9%), Dermatological (8.8%) and Genitourinary (8.8%). So while there are no seismic shifts in therapeutic focus on display, there are clearly fairly substantial variations in growth rates when the pipeline is dissected in this manner.

There are also two 'non-therapeutic' groups displayed in this graph, for Reformulations and Biotechnology. We'll return to the biotech drugs when we move to examine the types of drugs in the pipeline in the next section of this report, but the rise in reformulations of old drugs into novel delivery systems is more evidence of the increasing propensity for pharma companies to seek to thoroughly wring out every drop of value from their successes.

Moving to slice up the therapeutic pipeline more finely, we can look at the most popular of the 227 individual therapeutic categories used in Pharmaprojects/Pipeline, and these are displayed in Table 2. Immediately we can see the major source of the growth in Anti-infectives – third-placed Prophylactic vaccines have shot up over the past year, experiencing a spectacular 22.9% expansion in the number of candidates currently under development. Recombinant vaccines also rise, although some projects will be counted under both of these categories.

Table 2: Top 25 Therapeutic Categories

POSITION 2014 (2013)	THERAPY	NO OF R&D PRODUCTS 2014 (2013)	TREND
1 (1)	Anticancer, other	1834 (1759)	↑
2 (2)	Anticancer, immunological	989 (903)	↑
3 (3)	Prophylactic vaccine, anti-infective	644 (524)	↑
4 (5)	Antidiabetic	524 (489)	↑
5 (4)	Analgesic, other	515 (489)	↑
6 (7)	Recombinant vaccine	435 (386)	↑
7 (6)	Anti-inflammatory	427 (442)	↓
8 (10)	Ophthalmological	398 (359)	↑
9 (13)	Reformulations, fixed-dose combinations	395 (349)	↑
10 (8)	Cognition enhancer	382 (384)	↔
11 (14)	Immunosuppressant	361 (341)	↑
12 (18)	Monoclonal antibody, other	340 (273)	↑
13 (15)	GI inflammatory/bowel disorders	338 (315)	↑
14 (12)	Antiviral, other	337 (350)	↓
15 (11)	Cardiovascular	334 (351)	↓
16 (17)	Monoclonal antibody, human	321 (286)	↑
17 (16)	Musculoskeletal	314 (292)	↑
18 (9)	Recombinant, other	311 (381)	↓
19 (19)	Neurological	311 (269)	↑
20 (-)	Biosimilar	284 (-)	↑
21 (21)	Monoclonal antibody, humanized	280 (260)	↑
22 (24)	Antiasthma	264 (237)	↑
23 (20)	Neuroprotective	264 (266)	↔
24 (22)	Antiarthritic, other	254 (255)	↔
25 (23)	Antiparkinsonian	254 (250)	↔

Source: Pharmaprojects® Pipeline®, January 2014

We can also see the upward trend for the two leading cancer categories, and determine that the increase in Alimentary/Metabolic drugs is being fuelled for the large part by rises in R&D in Antidiabetics and drugs for GI inflammatory/bowel disorders. Ophthalmological drugs also posted a sizeable jump up the table. Away from disease-related therapeutic categories, there are several notable items in this table. Firstly, it seems that over the past year, Biosimilars have truly arrived. The category was first created just less than four years ago, but has now slammed into the Top 20, with 284 active drugs. This represents something of an explosion in development of these kinds of drugs, but some analysts have predicted that their time

in the sun may be short-lived, so it will be fascinating to see where they head next year. Original work in monoclonals also continues to rise. It's worth noting that the apparent decline in the general category for Recombinant drugs is somewhat artificial, since the creation of the new category for Fusion proteins saw many of these candidates migrate to this new class.

Next, in Table 3, we zoom in even further, to look at the individual diseases which are attracting the most attention from the industry currently.

Table 3: Top 25 Indications

POSITION 2014 (2013)	DISEASE*	NO. OF ACTIVE COMPOUNDS	TREND
1 (1)	Cancer, breast	440 (437)	↔
2 (2)	Cancer, colorectal	351 (347)	↔
3 (4)	Diabetes, Type 2	346 (336)	↑
4 (5)	Alzheimer`s disease	340 (331)	↔
5 (3)	Cancer, prostate	336 (340)	↔
6 (6)	Cancer, lung, non-small cell	324 (314)	↑
7 (7)	Arthritis, rheumatoid	322 (313)	↔
8 (8)	Cancer, pancreatic	289 (303)	↓
9 (9)	Pain, general	287 (292)	↔
10 (10)	Cancer, ovarian	279 (273)	↔
11 (11)	Cancer, melanoma	257 (246)	↑
12 (12)	Asthma	255 (224)	↑
13 (14)	Cancer, brain	212 (194)	↑
14 (17)	Cancer, liver	204 (176)	↑
15 (15)	Parkinson's disease	196 (186)	↑
16 (13)	Infection, hepatitis-C virus	188 (203)	↓
17 (20)	Psoriasis	182 (165)	↑
18 (24)	Chronic obstructive pulmonary disease	182 (145)	↑
19 (19)	Cancer, lymphoma, non-Hodgkin's	173 (172)	↔
20 (21)	Infection, HIV/AIDS	168 (161)	↔
21 (25)	Infection, influenza virus prophylaxis	168 (141)	↑
22 (23)	Cancer, leukaemia, acute myelogenous	164 (155)	↔
23 (16)	Pain, neuropathic	163 (177)	↓
24 (18)	Cancer, myeloma	162 (172)	↓
25 (22)	Cancer, renal	153 (160)	↔

*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® Pipeline®, January 2014

The trends identified further up the therapeutic activity spectrum, as usual, generally trickle down to the top diseases list. Within the set of cancer diseases in this table, most are flattish, but a couple of tumour types do stand out as showing particular pipeline expansion. Liver cancer R&D is up 15.9%, while brain cancer is just above in the list with an also impressive 9.3% inflation. Prostate cancer falls from third to fifth, albeit with a decline of just four drugs in its pipeline. Elsewhere, the significant increases in the respiratory area are revealed to be derived from growth in asthma and COPD R&D, and in the dermatological area from psoriasis. For those diseases showing decreases this year, it's interesting to see hepatitis-C drop after many years of rising. This comes just as the first of the new generation anti-HCV small molecules hit the market. The fact that this is likely to be a highly competitive area, in which Gilead has reportedly stolen a march, may not be entirely unconnected with a slight move away from R&D for this disease.

One other to note before moving on – there are no new entrants into this chart. The Top 25 diseases are exactly the same ones as last year. This looks like further evidence of the comparative stability seen in R&D in 2014.

What kinds of drugs are in the pipeline?

We've already noted the expansion of Biosimilars, but what other kinds of drugs and drug development strategies are gaining purchase or slipping back? Well, as Figure 6 has already shown us, in the broader area of Biotechnology drugs in general, there has been impressive growth this year. This year's figure of 3,123 drugs represents a 13.5% increase in the number of biotech drugs, which now account for 27.6% of all agents in development. The proportion has risen from 26.2% last year, when both the number and share had declined.

Also highlighted earlier was the uptick in monoclonal antibody R&D, and we can further investigate the kinds of drugs in the current pipeline by examining them by the class of active moiety via our Origin of Material data field. This classifies drugs broadly into chemically-synthesized, biologically-produced and naturally-derived drugs, and further subdivides them into more specific categories. The Top 25 Origins are shown in Table 4.

Table 4: Top 25 Origins of pipeline drugs

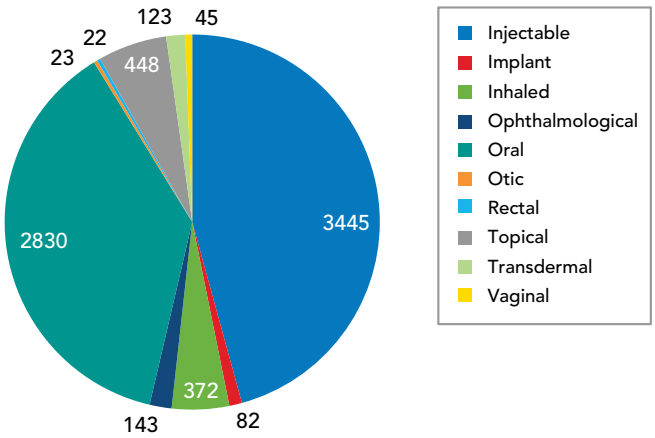
POSITION 2014	ORIGIN	NO OF ACTIVE DRUGS
1	Chemical, synthetic	6262
2	Biological, protein, antibody	1163
3	Biological, protein, recombinant	808
4	Biological, protein	367
5	Chemical, synthetic, peptide	346
6	Biological, virus particles	303
7	Chemical, synthetic, nucleic acid	285
8	Biological, nucleic acid, viral vector	228
9	Natural product, plant	151
10	Biological, peptide	136
11	Biological, cellular, autologous	122
12	Biological, nucleic acid, non-viral vector	118
13	Biological	113
14	Biological, peptide, recombinant	112
15	Biological, cellular, heterologous	99
16	Biological, bacterial cells	94
17	Chemical, semisynthetic	76
18	Biological, cellular	64
19	Biological, nucleic acid	48
20	Natural product, bacterial	44
21	Chemical, synthetic, isomeric	43
22	Natural product	37
23	Biological, other	27
24	Natural product, animal	26
25	Natural product, fungal	22

Source: Pharmaprojects® Pipeline®, January 2014

This shows that synthetic chemical small molecules are still by far the largest source of drug candidates, representing 55.4% of all pipeline drugs, although it is worth pointing out that when the origin of an agent is undisclosed, our default is to assume that it is in this class until we discover otherwise. Synthetic nucleic acids are the second most popular class of chemically-synthesized molecules. The data also confirms the popularity of antibody-based drugs, which now account for 10.3% of all candidates – a pretty remarkable percentage. The Top 10 also shows us that viral particles and nucleic acid delivered in a viral vector are other popular biological strategies, and that the most common sources of naturally-derived drugs are botanical.

One of the reasons why understanding the kind of drug a company is developing is important is that it can have huge bearing on the drug's delivery method. Figure 7 shows how the pharma pie is sliced up by major delivery route methods. Perhaps, surprisingly, there are currently more injectable drugs under development than there are oral ones, despite the fact that oral administration is clearly preferable to both the patient and the industry. (There is some bias introduced here again in the editorial process, in that a biological macromolecule can be assumed to be injectable and is therefore labeled as such, whereas a small molecule could be injectable or oral depending on its pharmacodynamics, and will therefore, in the absence of any further information, remain labeled as unknown (not shown)). Nonetheless, the small size of the proportion of oral molecules compared to the entirety of those with a known delivery route may raise a few eyebrows. Note, however, that drugs under development for use via more than one delivery method will be double-counted in this data.

Figure 7. Pipeline by Delivery Route



Source: Pharmaprojects® Pipeline®, January 2014

Lastly in our analysis, we move to looking at how the drugs in the pipeline are working and what they are targeting. Table 5 reports on how the landscape of the leading mechanisms of action assigned to the agents under development has shifted over the past twelve months.

Table 5: Top 25 Mechanisms Of Action (Pharmacology)*			
POSITION 2014 (2013)	MECHANISM OF ACTION (PHARMACOLOGY)*	NO. OF ACTIVE COMPOUNDS 2014 (2013)	% OF COMPOUNDS PR/R/L
1 (1)	Immunostimulant	1441 (1242)	9%
2 (4)	Immunosuppressant	185 (146)	31%
3 (2)	Angiogenesis inhibitor	169 (188)	17%
4 (7)	Opioid mu receptor agonist	132 (112)	26%
5 (5)	Apoptosis stimulant	119 (135)	10%
6 (8)	DNA inhibitor	110 (107)	16%
7 (17)	Tumour necrosis factor alpha antagonist	94 (72)	15%
8 (19)	Glucocorticoid agonist	93 (70)	35%
9 (20)	PI3 kinase inhibitor	86 (70)	1%
10 (9)	Cyclooxygenase 2 inhibitor	81 (92)	42%
11 (13)	Vascular endothelial growth factor (VEGF) receptor antagonist	77 (80)	19%
12 (15)	DNA topoisomerase II inhibitor	72 (74)	24%
13 (18)	Cyclooxygenase 1 inhibitor	64 (71)	47%
14 (10)	Tubulin inhibitor	64 (88)	11%
15 (-)	DNA synthesis inhibitor	62 (-)	31%
16 (3)	Cell cycle inhibitor	62 (147)	27%
17 (-)	Opioid delta receptor agonist	62 (-)	26%
18 (-)	Gene expression inhibitor	60 (-)	0%
19 (-)	Opioid kappa receptor agonist	59 (-)	25%
20 (-)	T cell inhibitor	56 (-)	21%
21 (-)	Glucagon-like peptide 1 agonist	56 (-)	13%
22 (-)	Insulin secretagogue	55 (-)	44%
23 (-)	Microtubule stimulant	54 (-)	15%
24 (-)	Cell wall synthesis inhibitor	54 (-)	39%
25 (-)	Progesterone receptor agonist	54 (-)	44%

*This table is affected this year by a project we undertook to clean-up this data on our drug profiles following the introduction of our hierarchical mechanism of action classification a couple of years ago. This has removed some higher level mechanisms which were present on a drug in addition to more specific ones, so this is why the Top 25 here has appeared to have changed more than the others.

Source: Pharmaprojects® Pipeline®, January 2014

Therefore, it's perhaps more instructive to this year just focus on our table of the Top 25 targets (Table 6). This shows that the mu1 opioid receptor, a pain target, remains the single most popular protein to be hit by drugs in the pipeline, showing good growth and edging slightly further ahead of the second-placed glucocorticoid receptor. Tumour necrosis factor (a target whose name has been simplified by *Gene* in the past twelve months from the earlier 'tumour necrosis factor (TNF superfamily, member 2)') posts a sizeable increase, and with the kappa1 opioid receptor, completes a clean sweep of the Top 4 for targets involved in pain and inflammation. Elsewhere, another opioid receptor subtype, delta1, climbs the chart, indicating considerable research across the board in opioid class analgesics at present. Another high riser is the cancer target epidermal growth factor receptor, up three places to just enter the Top 10. PI3Kα is another currently voguish cancer target to be seen shooting up the charts. The more old-school beta tubulin can be seen headed in the opposite direction.

Table 6: Top 25 Drug Protein Targets		
POSITION 2014 (2013)	TARGET	NO. OF ACTIVE COMPOUNDS 2014 (2013)
1 (1)	Opioid receptor, mu 1	155 (131)
2 (2)	Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)	121 (98)
3 (9)	Tumour necrosis factor	91 (69)
4 (7)	Opioid receptor, kappa 1	87 (72)
5 (4)	Polyprotein, hepatitis-C virus	86 (90)
6 (3)	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) [*COX-2*]	85 (94)
7 (8)	Insulin receptor	82 (70)
8 (5)	Prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase) [*COX-1*]	81 (85)
9 (6)	V-erb-b2 avian erythroblastic leukemia viral oncogene homologue 2 [*Her-2*]	79 (83)
10 (13)	Epidermal growth factor receptor	77 (63)
11 (18)	Opioid receptor, delta 1	67 (52)
12 (10)	Gag-pol, HIV-1	65 (68)
13 (11)	Dopamine receptor D2	65 (67)
14 (14)	Adrenoceptor beta 2, surface	65 (60)
15 (-)	Progesterone receptor	62 (-)
16 (16)	Estrogen receptor 1	59 (57)
17 (21)	Mechanistic target of rapamycin (serine/threonine kinase) [*mTOR*]	58 (48)
18 (15)	Kinase insert domain receptor (a type III receptor tyrosine kinase) [*VEGFR2*]	57 (58)
19 (25)	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha [*PI3K*]	57 (43)
20 (17)	Glucagon-like peptide 1 receptor	56 (57)
21 (19)	Amyloid beta (A4) precursor protein	55 (51)
22 (12)	Tubulin, beta class I	53 (66)
23 (24)	Vascular endothelial growth factor A	52 (46)
24 (22)	Membrane-spanning 4-domains, subfamily A, member 1	50 (48)
25 (23)	Solute carrier family 6 (neurotransmitter transporter), member 4 [*CD20*]	50 (48)

Source: Pharmaprojects® Pipeline®, January 2014

By January 2014, 2,541 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 2,498 remain so. This indicates that 68 novel targets were identified in the past twelve months – a figure which is lower than the 89 through 2012 and lower still than the 179 observed the previous year. Is innovation decelerating? If so, this is perhaps the one worrisome feature of this year's clutch of statistics. In terms of the number of targets which currently are the focus of active drug development, this now stands at 1,443, and has risen more (from 1,416) over the past year than it did over the previous twelve months (from 1,404). So it's difficult to form an entirely negative conclusion even here.

Developing more, spending more

So despite this slight final note of caution, there is every indication here that the industry should be clinking those champagne glasses once again. With a tumescent pipeline, swollen at every stage, and relative stability in corporate manoeuvrings, this looks like the best set of data seen in many a moon. But while it's certainly more indicative of a healthy industry than universal declines, a bigger pipeline, taken in isolation, just tells us that the industry is currently spending more money. And with R&D costs per compound still spiraling, pharma continues to be bedeviled by high failure rates. A recent paper by colleagues at our sister company, Sagient Research, published in January 2014's edition of Nature Biotechnology (Vol 32(1), pg 40), reports that across 835 drug developers from 2003-2011, while 64% of compounds made it from Phase I through to Phase II, only 32% passed from Phase II into Phase III. The overall subsequent approval rate for drugs in Phase I was just 10.4%. So an awful lot of cash is still going down the drain, while, even though the numbers seesaw up and down from year to year, the long term trend for delivery of new drug approvals has stayed resolutely flat. To most, this would seem to be an ultimately unsustainable business model. So before we backslap the industry too much, we should examine 2013's output of new active substances, something we will be doing in our supplement to this report to be published in March 2014, once we have established the truly definitive list. Look out for that final piece of the jigsaw.

So before we backslap the industry too much, we should examine 2013's output of new active substances, something we will be doing in our supplement to this report to be published in March 2014, once we have established the truly definitive list.

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