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White Paper

Pharma R&D Annual Review 2023

by Ian Lloyd, Senior Director, Pharmaprojects at Citeline

Reimagining the future
one chapter at a time

April 2023

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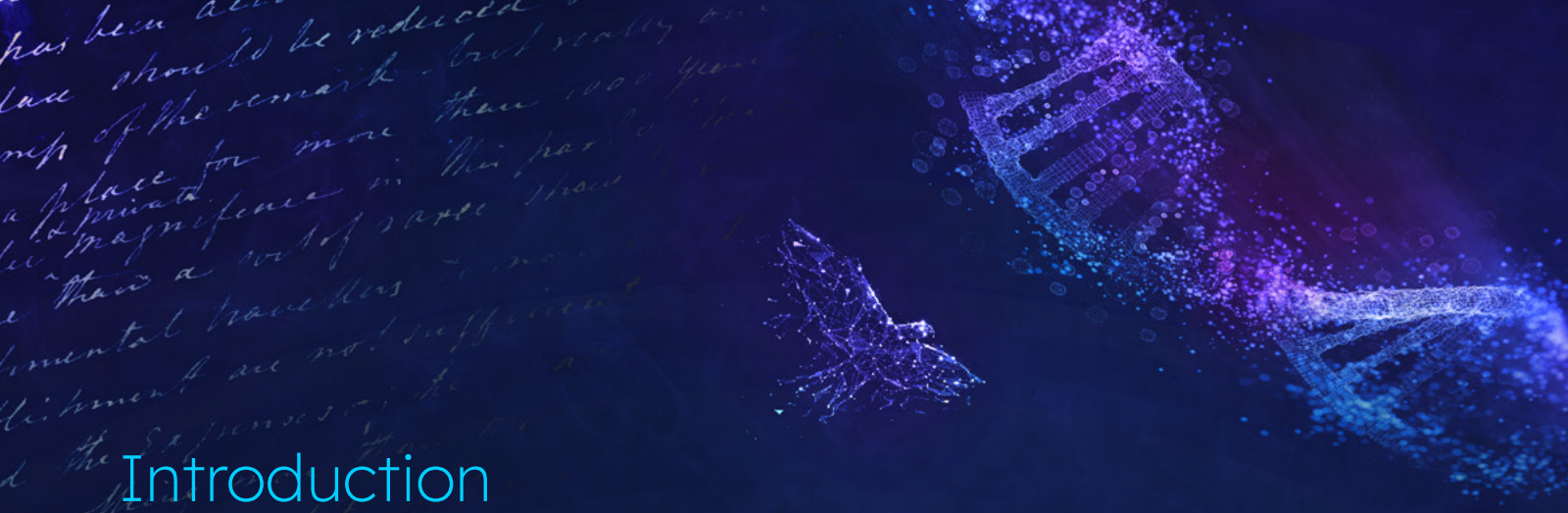

Introduction

Welcome to Pharmaprojects' 2023 review of trends in pharmaceutical R&D. For over 30 years now, I've been taking an annual look at the evolution of pharma R&D, and in this article, I'll examine the state of play at the start of 2023. We'll assess industry trends by examining the pipeline by company, therapeutic area, disease, target, and drug type, using data from primarily Pharmaprojects, part of the Citeline suite of products, which has been tracking global drug development since 1980. This report will be followed up by our annual supplement reviewing the New Active Substance launches for the year just passed. But here, we'll tell the story of pharma R&D as it is today: an epic tale, with a rich cast of characters and a global scope, and no doubt a number of unexpected plot twists. Hopefully, it will be a real page-turner!

Regular readers of this report (which has been running since 1993, so is presented here in its 31st edition) will know that in recent years, I've threaded a different theme through each edition, to highlight points, to draw analogies, and to add a little character into what could otherwise be a rather lengthy narrative through a potentially dreary parade of statistics, charts, and tables. Themes selected so far have included astronomy, movies, the natural world, music, food and drink, science fiction, and, last year, travel. This year, I decided to make a few nods to the world of literature and books to help illustrate my points. Storytelling is as old as humanity itself, and fiction has always been used as a proxy to help us to understand the real world. The best literature enlightens, thrills, amuses, and engages the reader. I'm certainly no Shakespeare, but I hope that my words will throw some light on the current state of the pharmaceutical industry, in the same way that a great novel does on the human condition.

So, what will be my opening lines to this year's magnum opus? A memorable set of bon mots to pique the interest of the reader is important. Various online polls pick different books as having the best attention-grabbing first sentences, but a number come up regularly in top 10s, so there is some degree of consensus of what constitutes a classic first sentence construction. Among those repeatedly cited are: "It is a truth universally acknowledged, that a single man in possession of a good fortune, must be in want of a wife" — Jane Austen, *Pride and Prejudice (1813);* "It was a bright cold day in April, and the clocks were striking thirteen" — George Orwell, *1984 (1949);* "If you really want to hear about it, the first thing you'll probably want to know is where I was born, and what my lousy childhood was like, and how my parents were occupied and all before they had me, and all that David Copperfield kind of cr*p, but I don't feel like going into it, if you want to know the truth" — JD Salinger, *The Catcher in the Rye (1951)*, and "All this happened, more or less" — Kurt Vonnegut, *Slaughterhouse-Five (1969)*. But perhaps one of the most famous opening lines to a novel in history which best describes the experience of pharma over the past few years can be borrowed from Charles Dickens' seminal 1859 opus, *A Tale of Two Cities:* "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair."

Of course, it's the COVID-19 pandemic that I'm thinking of here. A globally cataclysmic event, it threw the entire world into turmoil, and placed the pharmaceutical industry firmly at the center of the action. Suddenly, drug R&D was supposed to ride to a heroic rescue, but at the same time, a whole set of new barriers were being thrown in the way of its delivering the much-desired happy ending. Clinical trials had to be paused, lab workers found themselves marooned at home, and the whole script for drug development had to be rewritten.

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Introduction Continued

But, as any good author will tell you, without jeopardy, there's no tension and thus no story. What has followed, during a time when many of us felt like we were living through a dystopian drama worthy of Margaret Atwood, was an almost Homeric quest for a solution to an almost unprecedented crisis. With the stoicism worthy of Thomas Hardy's Gabriel Oak *(Far from the Madding Crowd, 1874),* the industry hunkered down and just got on with it. Almost unbelievably, the golden fleece of a vaccine was found in an incredibly short timespan — its discovery turned out to be more a novella than the expected *War and Peace*-like weighty tome by Leo Tolstoy (1869) — like weighty tome — allowing the world to return rapidly to some kind of normality, and the pharma industry to emerge as a Gandalf-ish wizard leading the people to peace and prosperity. At the time of writing, in January 2023, it feels, in the West at least, as though this dark episode in our lives has largely drawn to a close. However, with China unexpectedly and suddenly abandoning its much-vaunted but ultimately disastrous zero-COVID policy, the story has clearly not quite finished its final act. It is expected that China will now undergo the biggest waves of infection which the world has yet seen. Quite apart from the devastation likely to be wreaked domestically, the consequences for the world at large remain to be seen. There's nothing that the coronavirus likes more than a huge cast of supporting characters in which to ferment the potential curveball of a new variant. As serialized novels often state, To be continued…

But it appears that the pharmaceutical industry is emerging from this tumultuous episode stronger and emboldened, and, while maintaining an independent critical eye, to misquote Shakespeare's *Julius Caesar* (1599): "Friends, Romans, countrymen: We are here (largely) to praise pharma, not to bury it." Trends in the pharmaceutical industry can be as opaque to the onlooker as that famously unreadable novel, James Joyce's *Ulysses* (1922), so my aim here is to unravel all the competing and conflicting plot strands threading through the story of pharmaceutical drug development as it stands at the start of 2023. Think of me as the literary critic adding companion notes and explainers to the main text of the tale. I'm hoping that my text will serve as footnotes or an explanatory commentary which will help you untangle the story of R&D today, its characters and its nuances.

In many ways, each drug undergoes a journey like any literary character. We are introduced to each new molecule at the start of the story during its preclinical development, where we find out about its defining qualities, its strengths and weaknesses, and its potential role in the emerging story. As we go through the clinical stages of development, some drugs move forward, their narrative enhanced by positive outcomes, whereas some stumble and fall on *Hard Times* (Charles Dickens, 1854), and other characters are completely killed off. As the will-they-won't-they plotline reaches its denouement, the dramatic tension climaxes as we wait to see whether the powers-that-be will give us that longed-for happy ending, or seal the drug's fate to a more downbeat final act. If *All's Well That Ends Well* (William Shakespeare, 1623), the pharma companies responsible for our molecule's success will soon be embarking on a sequel.

So, settle down in your favorite chair, pour yourself a mug or a glass of whatever is your chosen tipple, and let's open the pages on the story of 2023. Guiding you through the cast of characters and the inevitable twisty-turny plot, I'll be your narrator. If you're sitting comfortably, I'll begin.

"The beginning is always today"

Mary Shelley, *Short Stories Vol. II* (2014)

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Chapter One – An Introduction: Total Pipeline Size

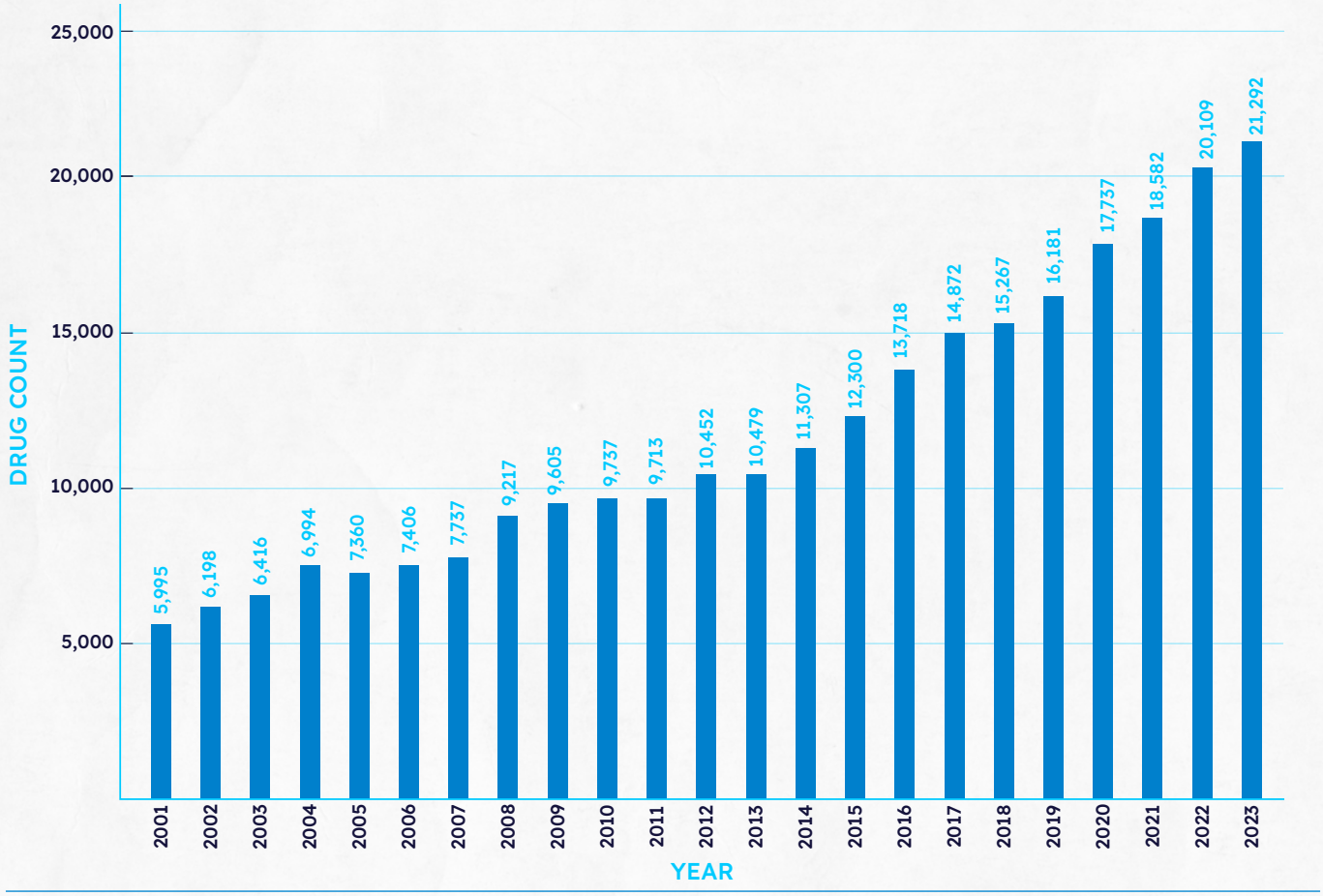
Pharma's story has a bigger word count than ever

As a forward to this year's tome, let's set the scene with an overview of the scope of our story — something akin to the maps of Middle Earth often presented in the frontispieces of the novels of J.R.R. Tolkien — by looking at the total number of drugs currently in the R&D "pipeline." All of the analyses in this report will be focusing on this set of drugs, so it's worth starting off with a definition of what we exactly mean by the term "pipeline." Here, we are counting all drugs in development by pharmaceutical companies, from those at the preclinical stage, through the various stages of clinical testing and regulatory approval, and up to and including launch. Launched drugs are still counted, but only if they are still in development for additional indications or markets. Drugs whose development has been terminated, or is complete, are not included. All data were collected on 3–4 of January 2023.

With the past few volumes of the drug development saga so full of incident and intrigue, now is perhaps the time to take stock and get some perspective on where our world is and its direction of travel. Figure 1 certainly shows that this episode has once more increased its word count, as the overall pipeline size has again hit a new high, with 21,292 drugs in development. This represents a 5.89% expansion of 2022's number, which is admittedly a lower growth rate than that seen last year of 8.22%. However, it is up from 2021's 4.76%, and, crucially, is not lagging far behind the 6.90% which is the five-year average growth rate. So, perhaps it is a more stable and sustainable increase as pharma settles down after the dramas of the past three years.

FIGURE 1: **Total R&D pipeline size, by year, 2001–23**

Source: Pharmaprojects®, January 2023



This means that there are 1,183 more drugs in development than there were this time last year, compared to the 1,527-drug rise seen last year, and the 845-drug uplift reported the year before. In total, 5,082 new drugs were added to the Pharmaprojects database during 2022 — considerably fewer than the 6,343 added during 2021. But there was definitely something of a "COVID-bounce" contribution to that year's figure, as last year's number was still in excess of the 2020 number of 4,730. As our continuous reviews of companies' pipelines get ever more up to date, it certainly feels like adding around 5,000 new drugs each year is a truer representation of the number of new candidates advanced into development in a 12-month period.

But, as noted earlier, the size of our subject material is not just governed by additions, but also by what has been edited out. To end up with a net surplus of 1,183 drugs, having added 5,082 drugs, must mean that 3,899 candidates exited (pursued by a bear?) the R&D pipeline. During 2022, 282 drugs were confirmed as being discontinued (up from 2021's 221), while a further 3,804 were moved out of the "Active" dataset as a result of being marked as "No development reported" (down from 4,658 the previous year — note that the figures don't exactly sum as drugs can move in and out of development in a single year). Overall, there was somewhat less churn seen during 2022, although the rate of flux is still pretty remarkable.

Of our new protagonists, where are their primary allegiances? Over 40% of newly identified drug candidates — 40.7% to be precise — are targeted against at least one form of cancer. This is up from the previous year's figure of 38.8%, leaving neurologicals, with 13.5%, a distant second. Interestingly, 19.5% of new candidates are focused on one or more rare disease — a significant rise on the 2021 figure of 17.5%. In terms of which companies contributed the most to the increased word count, it's fascinating to note that for the first time it was a Chinese company, Jiangsu Hengrui Pharmaceutical, leading the pack here. The more traditional contributors Pfizer and Roche followed next. As regards to the location of development of 2022's batch of neophyte drugs, the US is still far out in front with 1,840 candidates, but China is coming up on the rails with 1,457. Of course, we'll be examining the pipeline as a whole by all of the above measures in much more detail later.

So, this year's book of R&D is even more of a door-stopping magnum opus than ever. As always, we caveat the excitement at a bigger-than-ever pipeline with the warning that the vast majority of these drugs are still prelaunch, so are costs with risks attached rather than successful revenue-generators curing patients. 2021 once again was a record-beater in terms of the number of New Active Substances (NASs) successfully debuting onto the market, with 97 — far outstripping the previous record of 82 seen in 2020. Can 2022 come close to keeping up with this phenomenal output? It's possible: so far, we are reporting around 60 NASs for 2022, about the same number we saw at the same point last year. As we further refine our data towards the spring publication of our annual NAS Supplement, it will certainly be interesting to see if 2022 can get within touching distance of 2021. After all, a bigger novel is only better if it satisfies the reader more.

"I believe there is a theory that men and women emerge finer and stronger after suffering, and that to advance in this or any world we must endure ordeal by fire"

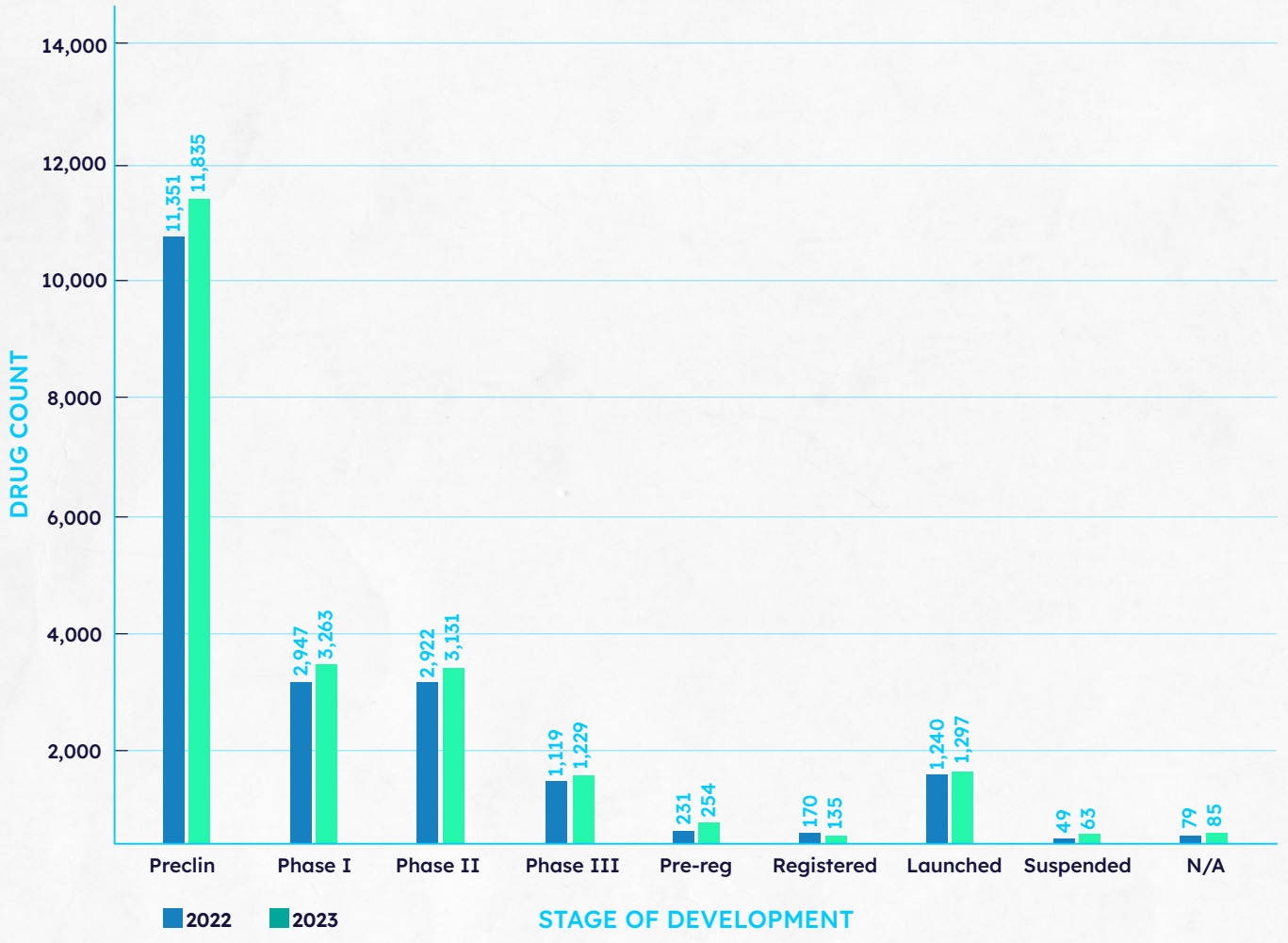
Daphne du Maurier, *Rebecca* (1938)

Pharmaceutical R&D, like great literature, has a beginning, a middle, and an end. This classic three-act structure is often cited as the overarching template for any work of fiction, and has famously been adopted by the movie industry. Of course, most books are really more complex than that. Similarly, arguably, drug development has three major "acts": preclinical, clinical, and regulatory, which can be broken down into smaller sections — the phases of development we use here in Pharmaprojects.

Figure 2 breaks down the 2023 pipeline by the drugs' current global statuses. Global status is the most advanced stage of development each drug has reached in any country, for any disease, and by any company, so each drug is counted only once here. What's immediately striking is that our 5.89% overall increase in pipeline size this year is spread fairly evenly throughout the phases of development. This hasn't always been the case historically: 2022 was more typical in that larger increases were seen at the earlier stages of R&D, declining as the story unfolded. Indeed, last year, the number of drugs in preclinical grew by a sizeable 11.0%; this year, that rate is down to a more manageable 4.3% — actually below the overall rate of increase for once. This might reflect the effect of our review process becoming more up to date and thus a greater proportion of preclinical drugs being moved to the inactive "No development reported" status.

FIGURE 2: **Pipeline by development phase, 2023 vs. 2022**

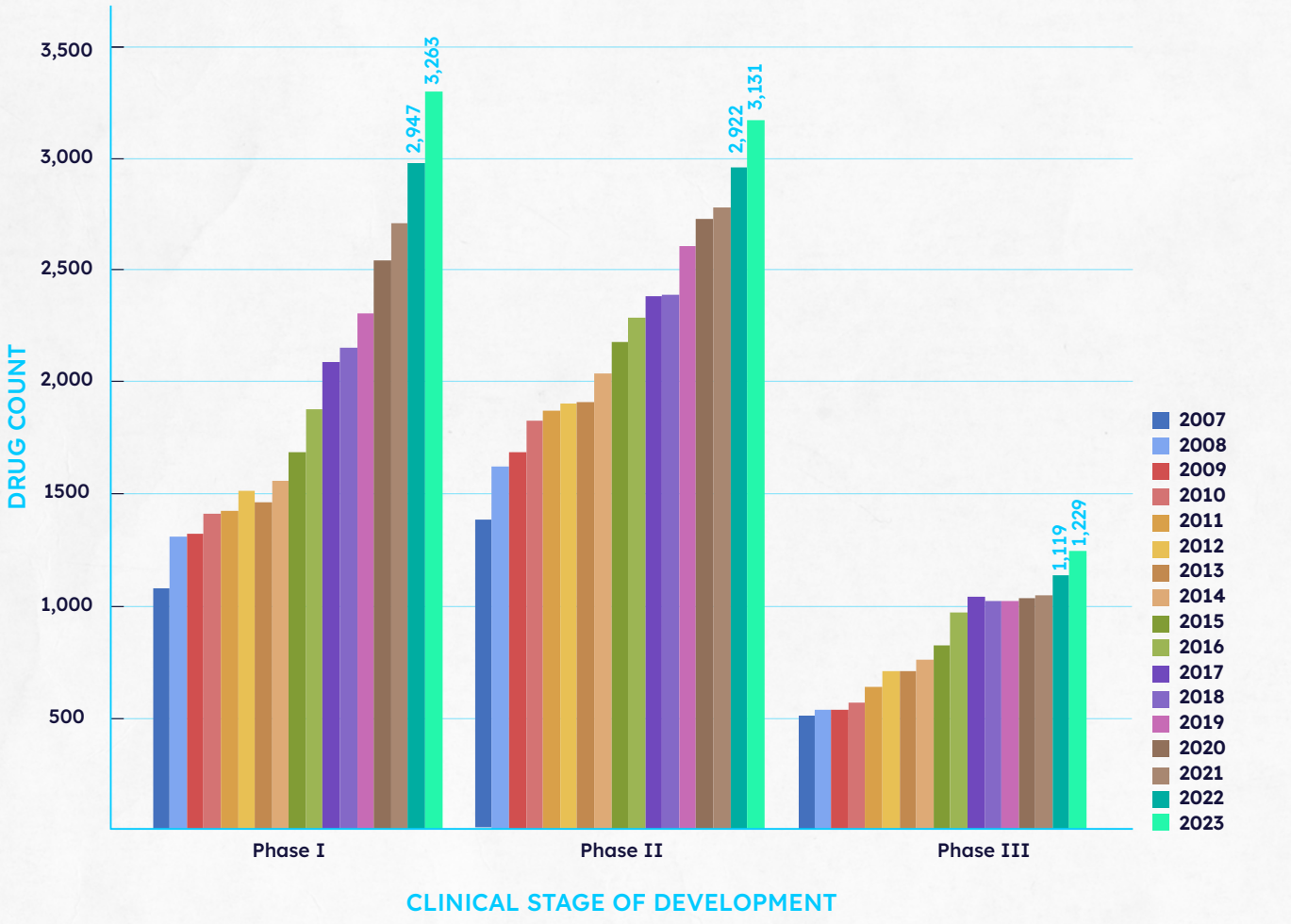
Source: Pharmaprojects®, January 2023 - (N/A = not applicable and is applied to companion diagnostics prelaunch)



In contrast, the number of drugs in Phase I clinical trials has gone up by a larger percentage, the 2023 rate coming in at 10.7%, higher even than the 10.1% seen last year. The number of drugs at Phase II also showed a bigger increase this year, up 7.2% compared to 6.4% in 2022, and Phase III was up by 9.8%, outpacing the 8.7% seen the year before. So, on the face of it, these are very healthy numbers. Note that these data are a snapshot in time: the fact that there are roughly the same numbers of drugs in Phase II as there are in Phase I in no way means that virtually all drugs undergoing Phase I then progress serenely to Phase II. In fact, there is considerable attrition between the two phases, but as Phase II development generally takes much longer, drugs "pile up" at the Phase II stage. It's a bit like how a traffic jam builds up when the motorway goes down from three to two lanes. Figure 3 gives you a slightly wider historical context, really highlighting how the Phase I and Phase II numbers have taken off in recent years, and showing how Phase III has returned to growth after a few moribund years. The second act of our pharma R&D novel seems to be getting bigger, although it's no doubt as packed with incident as ever.

FIGURE 3: **Clinical phase trends, 2007–23**

Source: Pharmaprojects®, January 2023



However, once again, it's good to question whether more always means better. After all, more drugs in clinical trials means more costs, and this could be a reflection of there not being more candidates, but it could be that the existing candidates are spending longer getting through a phase, which would clearly be a negative. A new report from the Deloitte Centre for Health Solutions titled "Seize the digital momentum: Measuring the return from pharmaceutical innovation 2022" certainly hints towards the latter, calculating that average cycle times — the time it takes for a new drug to progress from starting clinical trials to approval — increased to 7.09 years in 2022 from 6.9 years in 2021. At the same time, the team there estimated that the average cost of developing a drug, including the cost of failure, increased from $1,986 million in 2021 to $2,284 million in 2022. Taken together, Deloitte reported a fall in return on investment in pharma R&D. Now, admittedly, this report is based on a study at 20 leading biopharma companies, so is not necessarily giving an industry-wide picture. But it does serve to illustrate the fact that it's always wise not to take everything at face value. Just as in a good book, things may be not quite what they appear to be initially. Things are seldom as simple as they seem, and it's always wise to take a peek behind the wizard's curtain.

"Character cannot be developed in ease and quiet. Only through experience of trial and suffering can the soul be strengthened, ambition inspired, and success achieved"

Helen Keller, *The Open Door* (1902)

Chapter Three – Dramatis Personae: Top Companies

Main characters take a smaller role in our cast of thousands

Becoming a novelist is something which many of us dream of. A whole industry exists around offering advice and training courses on what makes a good read and what are its essential ingredients. We've already discussed the importance of an attention-grabbing opening, and of having an overall structure to your tale. One attribute that you'll find every novel-writing "expert" includes in their list is the need for a diverse and well-developed set of characters. Who could fail to be entranced by the deductive genius of Sherlock Holmes, the murderous artifice of Tom Ripley, or the elaborate construct that is Jay Gatsby's life? The characters of a great literary novel are not just vessels for the author to tell their story — they are the story.

The characters in our tale of pharma R&D have to be the pharmaceutical companies themselves. But who are the leads who cast the longest shadows over our story? Table 1 lists the top 25 companies by pipeline size, and it seems that we have a new main character: Roche. The Swiss giant usurps its compatriot Novartis, ending the latter's reign of six years at the top. It would seem that Roche's ascent is largely organic — it only posted one small acquisition during the past calendar year, that of

TABLE 1: **Top 25 pharma companies by size of pipeline**

Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	COMPANY	NO. OF DRUGS IN PIPELINE 2023 (2022)	NO. OF ORIGINATED DRUGS 2022	TREND
1 (2)	Roche	194 (200)	110	↔
2 (1)	Novartis	191 (213)	112	↓
3 (3)	Takeda	178 (184)	61	↔
4 (4)	Bristol Myers Squibb	175 (168)	96	↔
5 (5)	Pfizer	171 (168)	105	↔
6 (8)	Johnson & Johnson	156 (157)	84	↔
7 (6)	AstraZeneca	155 (161)	85	↔
8 (7)	Merck & Co	151 (158)	72	↔
9 (9)	Sanofi	145 (151)	82	↔
10 (10)	Eli Lilly	135 (142)	64	↔
11 (11)	GSK	123 (131)	60	↔
12 (12)	AbbVie	122 (121)	45	↔
13 (16)	Jiangsu Hengrui Pharmaceuticals	106 (89)	96	↑
14 (13)	Boehringer Ingelheim	99 (108)	75	↔
15 (14)	Bayer	93 (105)	63	↓
16 (21)	Gilead Sciences	86 (72)	59	↑
17 (15)	Otsuka Holdings	85 (93)	42	↔
18 (17)	Amgen	79 (83)	58	↔
19 (36)	Novo Nordisk	77 (51)	52	↑↑
20 (18)	Eisai	74 (80)	39	↔
21 (22)	Regeneron	73 (68)	41	↔
22 (20)	Daiichi Sankyo	70 (75)	37	↔
23 (27)	CSPC Pharmaceutical	68 (62)	53	↔
24 (23)	Shanghai Fosun Pharmaceutical	64 (68)	43	↔
25 (24)	Biogen	63 (66)	18	↔

Good Therapeutics. The gap between the two Basel-based giants is very small though, and Novartis holds onto its crown as the company originating the most drugs. The rest of the top five remains unchanged, and indeed it's striking how many companies in the table have very similar pipeline sizes now to those posted in 2022, and how little movement there is in general.

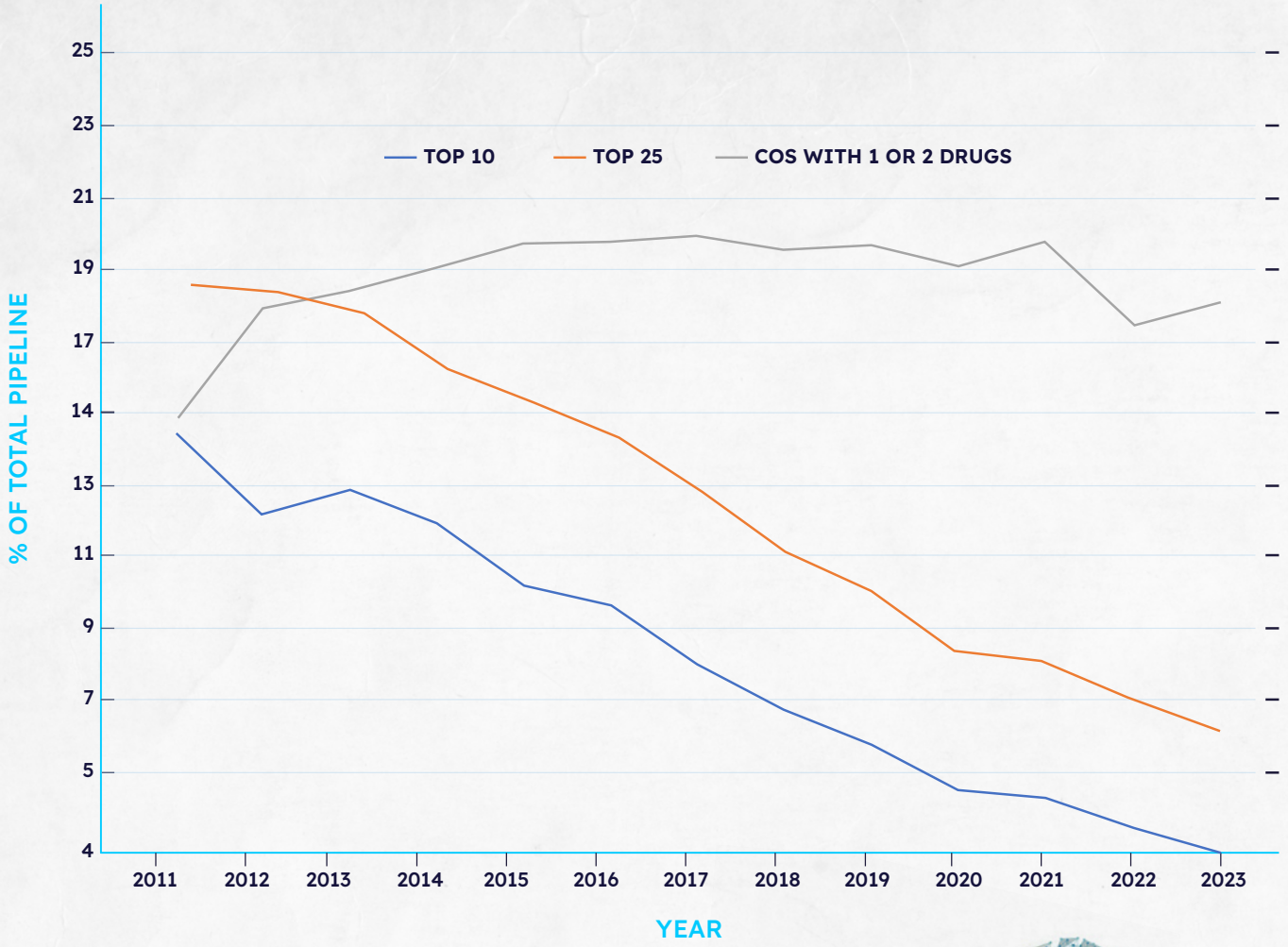
Notably, of the top 10, only Bristol Myers Squibb and Pfizer have larger pipeline sizes this year than last. This, and the overall lack of much change, can partly be accounted for by exceptionally low significant merger and acquisition activity during 2022. Aside from the aforementioned Roche transaction, Novartis acquired Gyroscope Therapeutics; Bristol Myers Squibb took over Turning Point Therapeutics; Pfizer purchased Biohaven Pharmaceuticals, ReViral, and Arena Pharmaceuticals; AstraZeneca absorbed TeneoTwo; Sanofi purchased Amunix Pharmaceuticals; and Eli Lilly bought Akouos. In the grand scheme of things, these acquired companies were only minor characters disappearing from the story, not materially affecting the size of their new parents' pipelines to any great degree. Meanwhile, Takeda, Johnson & Johnson, and Merck & Co didn't report any deals of relevance.

The landscape for deals through 2022 remained low on incident, with only 81 mergers and acquisitions reported by Pharmaprojects during the year, a fall from 2021's 116, and continuing a downward trend. Many industry observers seem to think that 2023 might be the year when the M&A plot comes back to life. Quoted in Scrip, Richard Wilson, senior vice president at Astellas Gene Therapies, commented that, "During 2022, there was a common question of 'have we reached the bottom yet?' as we saw company valuations drop dramatically, corporate ambitions shrink and, sadly, valued employees laid off as companies reacted to the challenging macroeconomic environment. M&A feels poised to heat up a little more." Similarly, Sarah Howell, CEO of reformulation specialist Arecor Therapeutics, was also bullish: "I believe that we will see a surge in M&A in 2023 after a quiet 2022," she said. "Pharma are sitting on significant capital reserves and the model of accessing external innovation is still very much alive!"

The most significant increase in pipeline size within the top 25 comes once again from China, and from Jiangsu Hengrui. After a spectacular debut in last year's listing, it advances further, with a 19.1% increase in its R&D portfolio. But Chinese companies did not manage a major landgrab within the upper echelons as they did last year, with CSPC Pharmaceutical being the only Chinese debutant in the upper echelons. The only other new entry into the table is the more familiar face of Novo Nordisk. The Danish concern returns to the big time this year, having made two acquisitions during 2022, those of Dicerna Pharmaceuticals and Forma Therapeutics. Fading out of the main action this year are two Japanese firms: Astellas, which falls from 19 to 26, and Sumitomo Pharma, dropping from 25 to 28. Overall, I can't remember a year when there was so little change within the top 25 and I employed the ↔ symbol in the table so much. This should probably be viewed as a sign of stability rather than stagnation.

FIGURE 4: **Share of the pipeline contributed by top 10 companies, top 25 companies, and companies with just one or two drugs, 2011–23**

Source: Pharmaprojects®, January 2023

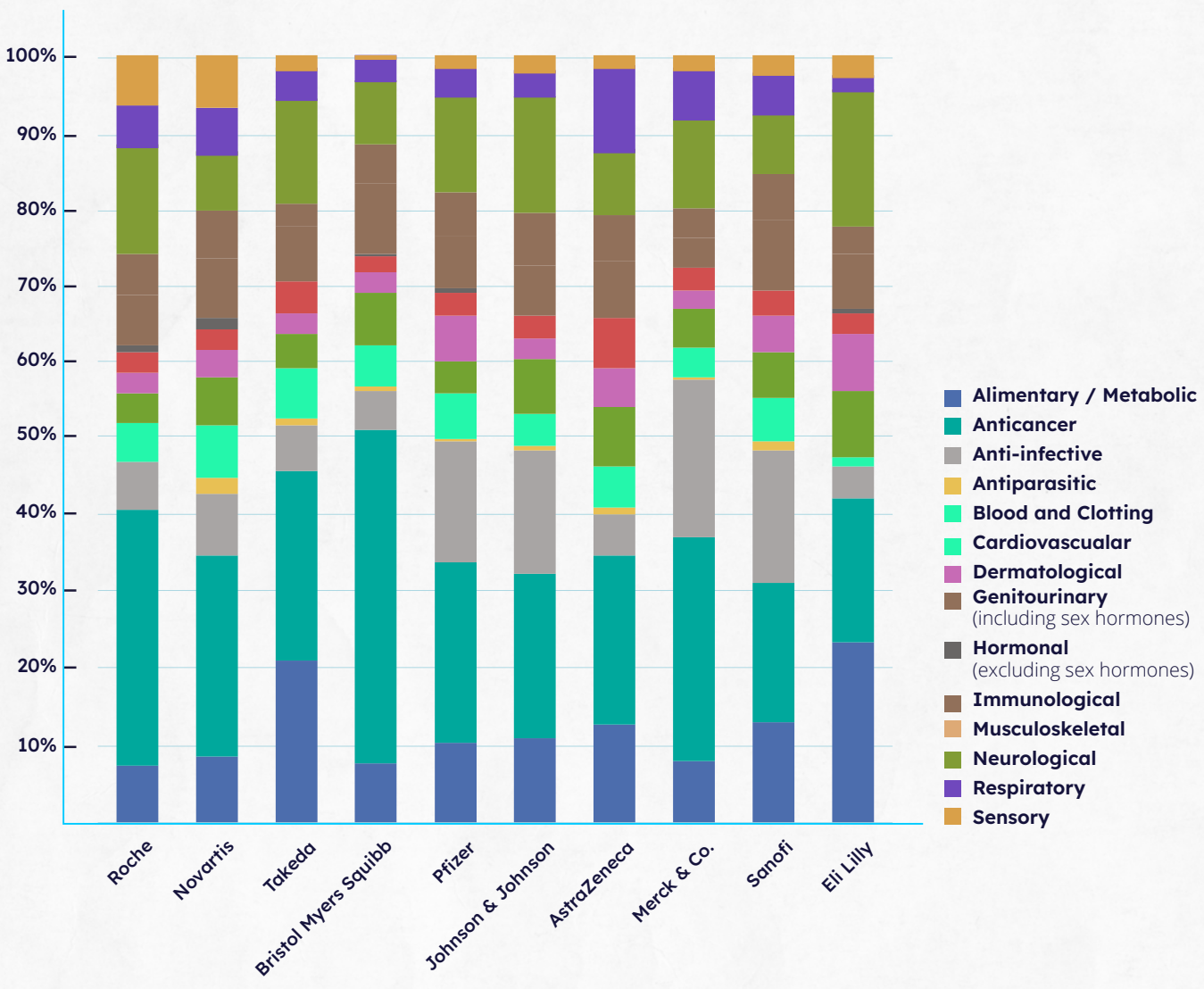


We've seen in previous years how our major characters are commanding a diminishing proportion of the overall word count, and this trend continues in 2023. As Figure 4 illustrates, the top 10 companies only originated 4.09%, a further significant decline from the 4.63% reported last year, whereas the top 25's share fell from 8.51% to 7.6%. The contribution made by the smaller supporting characters, the companies with just one or two drugs, rose, however, from 16.91% to 17.53%.

The leading lights of our novel do, however, have a rich and diverse set of character traits, as measured by the range of therapeutic areas in which they are involved, which is broken down in Figure 5. (Note that there is double-counting in this graph, as drugs can be in development for more than one disease area.) You can see that all of the major players still have interests across a multitude of disciplines. However, whereas last year, eight of the top 10 companies were developing at least one drug in all 14 therapeutic areas, this year, that number drops to three out of 10. However, for the other seven, they are each missing drugs in just one of the smallest therapeutic areas, namely hormonal products or antiparasitics. In another small but subtle shift, anticancers no longer form the largest therapeutic area for all 10 companies, as Eli Lilly is bucking the trend by having alimentary/metabolic as its primary focus. All of the companies are still putting significant resources into cancer though, whereas in some other therapeutic areas, such as anti-infectives, there is considerable variation in the size of their efforts. Bristol Myers Squibb remains the most oncology-focused of the 10.

FIGURE 5: **Disease focus areas of the top 10 pharma companies**

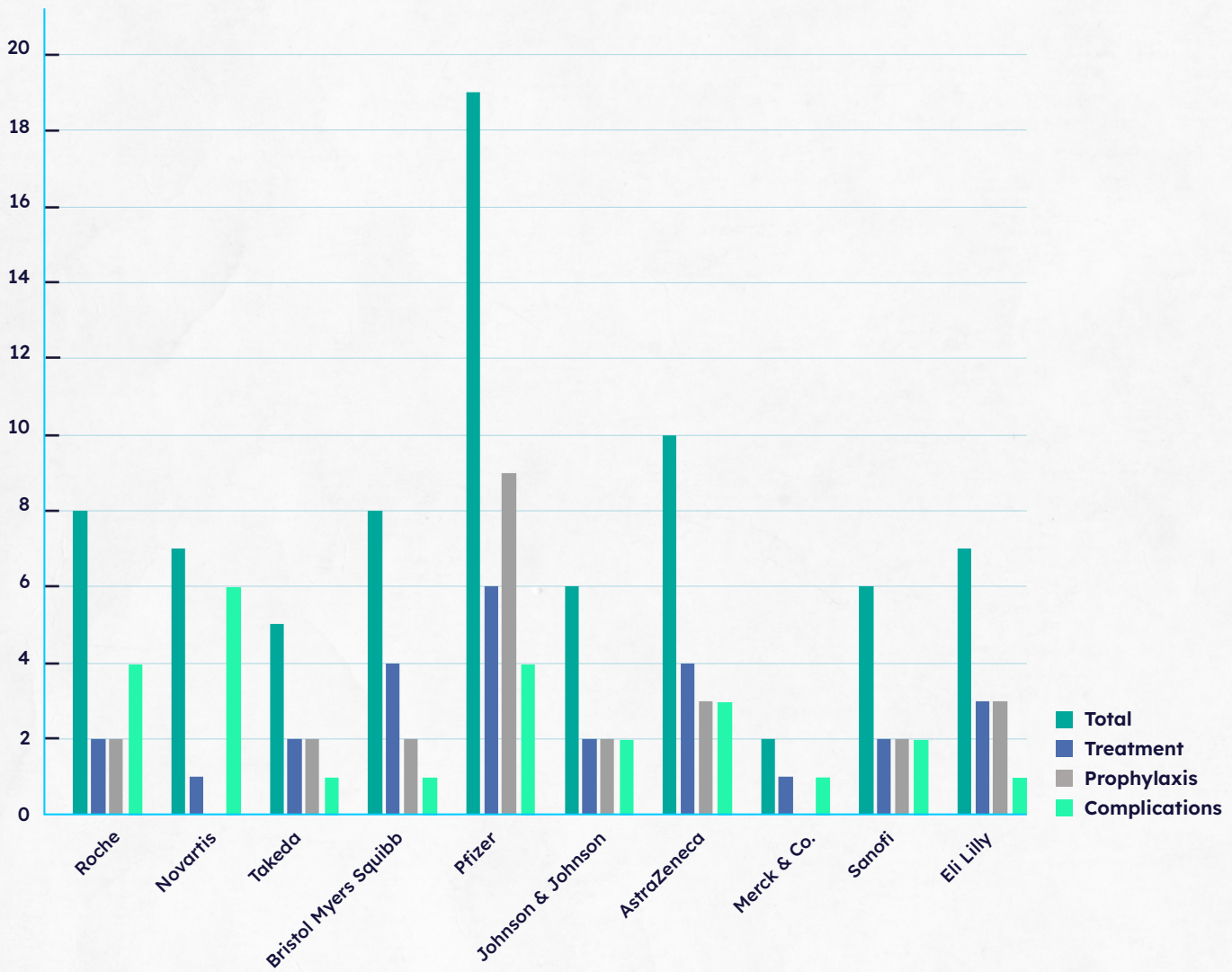
Source: Pharmaprojects®, January 2023



I'm hoping that this year will be the last that COVID-19 merits its own analyses in this report. However, just as Sir Arthur Conan Doyle tried to kill off his hero Sherlock Holmes by having him plunge over the Reichenbach Falls in *The Final Problem* (1893), only to find he had to resurrect him later due to his enduring popularity, the current deteriorating situation in China may mean that this proves not to be the case. While all of the top 10 still have some interest in drugs or vaccines against the virus which caused the global pandemic, it's becoming clearer now which of them are in it for the long haul, and for which activities look to be winding down. Pfizer is now the dominant force, with a total of 19 agents for treatment or prophylaxis of the infection, or for the management of its complications, up from 11 last year, followed by AstraZeneca with 10, up from eight. In contrast, Merck & Co's interest in this area has diminished to a meager two drugs (see Figure 6).

FIGURE 6: **COVID-19 pipelines at top 10 pharma companies**

Source: Pharmaprojects®, January 2023



In contrast, all but one of the top 10 (Sanofi being the exception) have a greater proportion of their pipelines focused on rare diseases than this time last year. Table 2 lists the top 20 companies by number of assets against rare diseases, and the top 10 pharma companies all appear in this table's top 12. Novartis holds the distinction of not only topping this table, but also having the greatest percentage of its pipeline targeting rare diseases among the Big Pharma beasts. Almost two-thirds of its drugs fall into this class, whereas at Eli Lilly the proportion is less than a third. Among companies in the next tier, Merck KGaA stands out with an eye-popping 84.6%. The niche player on the list, Medicines for Malaria Venture, has 100%, although this is because malaria is classified as rare based on its low incidence/prevalence in the US and EU — clearly, if you're in sub-Saharan Africa, this is sadly far from the case.

While most novels, and our immediately preceding analyses, focus on a relatively small number of main players, some books are famous — or maybe infamous — for having large casts of characters. Examples are weighty classics such as *Anna Karenina* (1878) and *War and Peace* (1869) by Leo Tolstoy, *Middlemarch* (1872) by George Eliot, and *Les Misérables* (1862) by Victor Hugo. More modern instances include *One Hundred Years of Solitude* (1967) by Gabriel Garcia Márquez, as well as the works of George R.R. Martin in the universe which spawned *Game of Thrones* (1996–). Our pharma industry similarly has a cast of thousands.

TABLE 2: **Top 20 pharma companies with a rare disease focus**

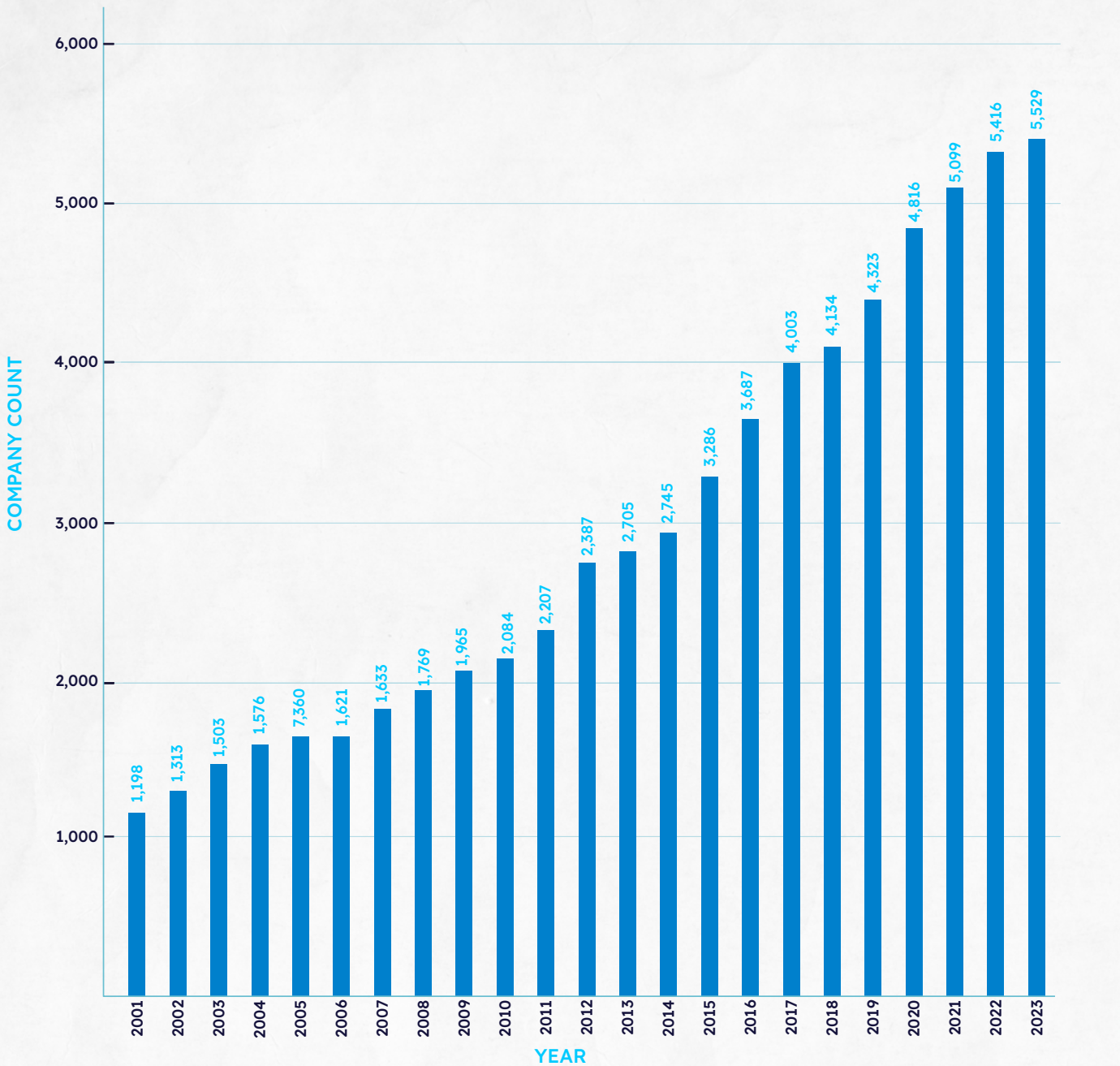
Source: Pharmaprojects®, January 2023

COMPANY	NO. OF DRUGS FOR RARE DISEASES	% OF PIPELINE
Novartis	127	66.5
Bristol Myers Squibb	115	65.7
Pfizer	109	63.7
Roche	97	50.0
Sanofi	91	62.3
Takeda	90	50.6
AstraZeneca	82	52.9
Johnson & Johnson	70	44.9
GSK	69	56.1
AbbVie	65	53.3
Merck & Co	56	37.1
Amgen	54	68.4
Bayer	44	47.3
Eli Lilly	42	31.1
Medicines for Malaria Venture	39	100.0
Otsuka Holdings	37	43.5
Biogen	36	57.1
Eisai	36	48.6
BeiGene	34	60.7
Merck KGaA	33	84.6

The total number of pharmaceutical companies involved in pharma R&D as of January 2023 came in at 5,529, a 2.1% increase over 2022's figure of 5,416. You can see from Figure 7 that this represents a considerable slowing of the rate of increase seen in 2021–22, which was 6.2%, but nonetheless represents a new high, and the figure overall has doubled over the past decade.

FIGURE 7: **Total number of companies with active pipelines, 2001–23**

Source: Pharmaprojects®, January 2023



Chapter Three – Dramatis Personae: Top Companies

Main characters take a smaller role in our cast of thousands

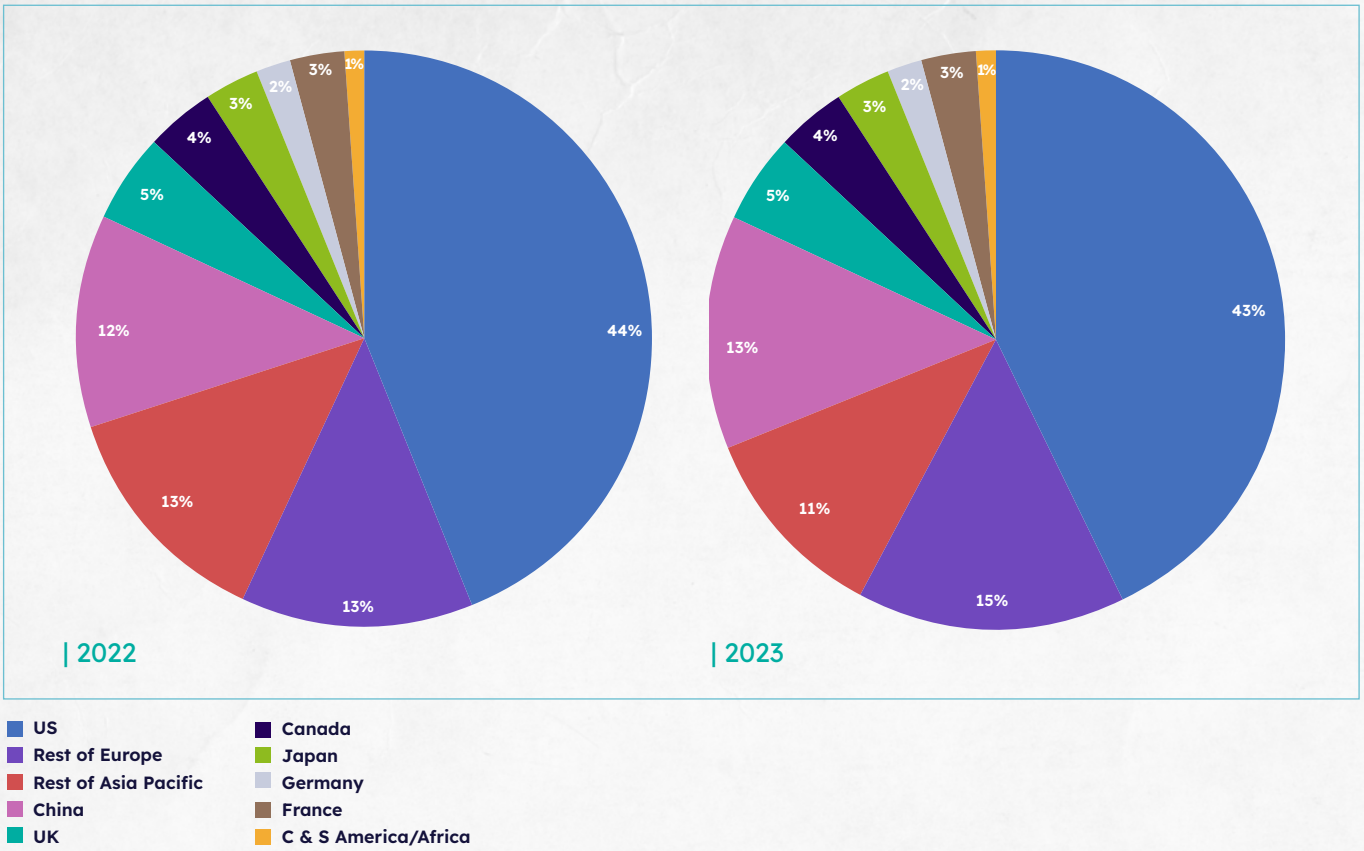
It looks like part of the reason that the increase in companies has slowed is due to fewer new companies being identified over the past 12 months, with 809 being added to the database. This is lower than the equivalent figure of 1,042 last year. With the overall number of companies only going up by 113, this means that a net total of 696 firms fell off the pages of the R&D book, a similar figure to last year's 725. While some of these firms may have failed or been acquired and have exited the narrative completely, others may reappear in sequels to this report because their disappearing act was based on a lack of new information on their drugs for over a year, and we will have therefore moved those drugs to "Inactive" for now and the company thus ceases to be represented as active. R&D companies that were once presumed missing or dead may be resurrected again later in the story, much like Sergeant Troy in Thomas Hardy's *Far from the Madding Crowd* (1874).

We've seen already that the background characters in pharma R&D provided an increased share of the overall pipeline in 2022, and an examination into their numbers reveals how. This year, we are reporting 825 companies with only two drugs in their pipelines, and a staggering 2,083 with just a single candidate. Both of these numbers are significantly up from their equivalent figures in 2022 of 759 and 1,833, respectively. Overall, these companies in minor roles in the background of crowd scenes of our story account for 52.6% of all pharma companies, a metric which is up on the previous year's 48.8%. No wonder their contribution has become greater.

While many books set their entire narratives in a very specific location, real or otherwise, others have a global reach, with fantasies, spy novels, and stories involving quests likely to have an international focus (think Ian Fleming's James Bond novels). Of course, the pharmaceutical industry is one of the most global of all, but what are the most used locations where characters in our story abide? The pie charts in Figure 8 break this down for 2022 and 2023. There are only subtle shifts over the past 12 months, with the US still the favored base, although losing a further 1% of share. Conversely, China picks up a percentage point, although with its total number of companies now standing at 808, only up a little from 2022's 792, there are signs that the explosion in the number of companies based there is starting to level off.

FIGURE 8: **Distribution of R&D companies by HQ country/region, 2022 and 2023**

Source: Pharmaprojects®, January 2023



While Figure 8 gives us the origins of our characters, where is the action actually taking place? Table 3 looks at all drugs in active R&D and where their development is reported to be taking place. Each drug is counted once for each country in which it is in development, so most drugs are being counted more than once here as they are in development in multiple countries. By this metric, the number of scenes set in the US has also declined somewhat, with 51.1% of all drugs reporting some US development this year, down from 53.4% last year. While the States is clearly still pre-eminent, again, China is creeping closer — its 23.6% share being up from 20.8% last year. Note that this table only lists countries with >1,000 drugs in development.

TABLE 3: **Where is R&D actually occurring?**

Source: Pharmaprojects®, January 2023

COUNTRY	NO. OF DRUGS	% OF PIPELINE
US	10,876	51.1
China	5,033	23.6
UK	3,048	14.3
South Korea	2,917	13.7
Germany	2,349	11.0
Canada	2,231	10.5
Australia	2,172	10.2
France	2,161	10.1
Spain	2,033	9.5
Japan	1,964	9.2
Netherlands	1,704	8.0
Italy	1,670	7.8
Belgium	1,651	7.8
Poland	1,575	7.4
Sweden	1,437	6.7
Denmark	1,415	6.6
Switzerland	1,403	6.6
Hungary	1,298	6.1
Czech Republic	1,283	6.0
Austria	1,258	5.9
Taiwan, China	1,240	5.8
Bulgaria	1,150	5.4
Finland	1,105	5.2
Ireland	1,085	5.1
Israel	1,062	5.0
Greece	1,055	5.0

North America
Asia
Europe
Oceania

Chapter Three – Dramatis Personae: Top Companies

Main characters take a smaller role in our cast of thousands

The overall takeaway this year is that, like in a long-running series of novels, most of our dramatis personae have remained the same from the 2022 to the 2023 editions. Changes to our cast of characters this year have been marginal, with most trends just advancing changes which have been under way for a number of years now. It's as if the pharma R&D story has a good formula — like an Agatha Christie whodunnit.

"The advantage of literature over life is that its characters are clearly defined, and act consistently"

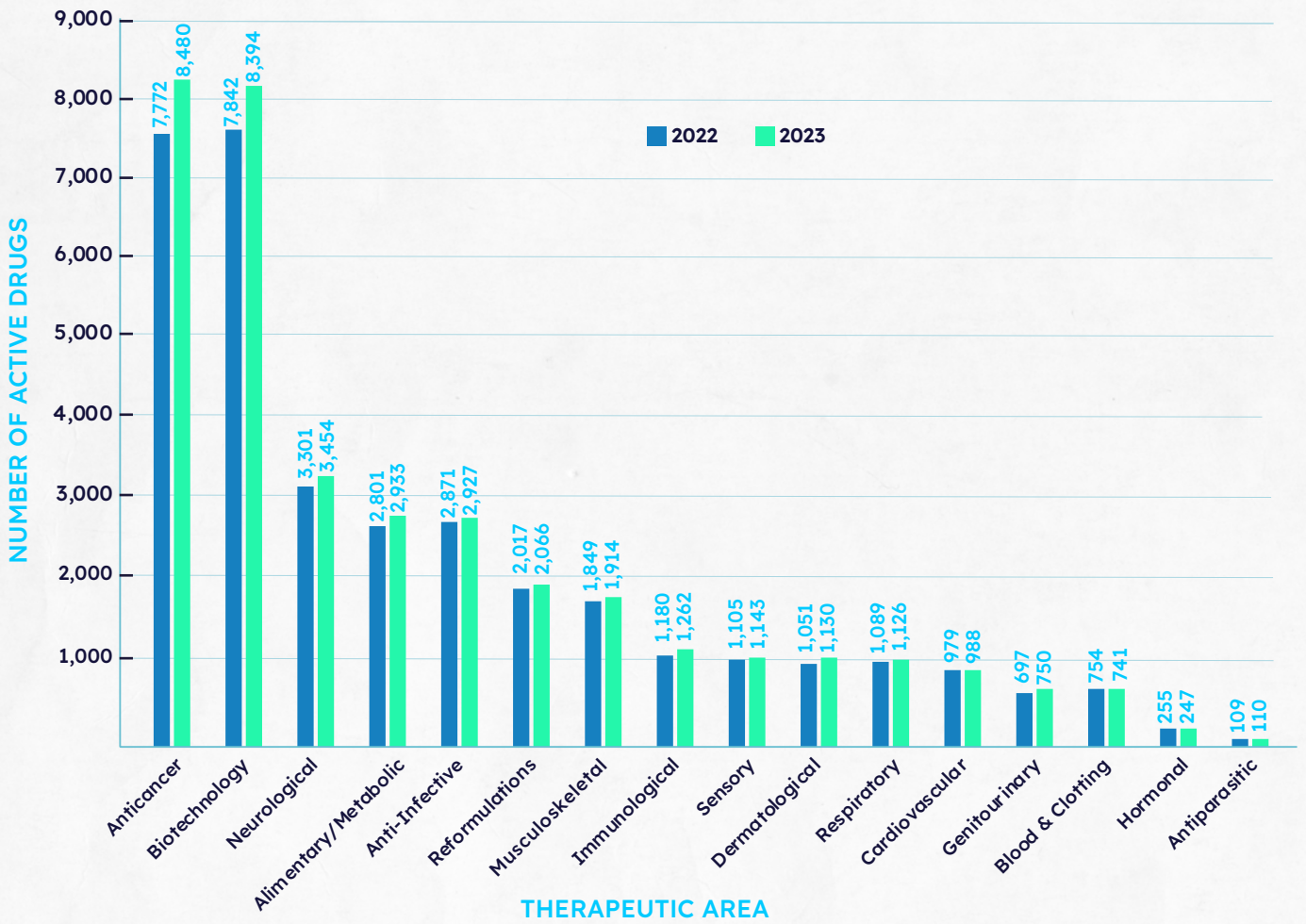
(Jerome K. Jerome)

Having established who our lead characters are, for our yarn to resonate with the reader, we need to look at their motivations and what they are hoping to achieve. This will propel the action and engage the reader, since a character doing something in a vacuum is not very interesting. For instance, the title character of Patricia Highsmith's *The Talented Mr Ripley* (1955) may be amoral, but because we understand why he is doing what he does, we are drawn along with it. This is analogous to understanding the therapeutic focuses of the pharmaceutical industry. What diseases is it trying to cure, where is its focus, and what is motivating it to develop the drugs it does?

As usual, we'll start with a bird's eye view, and then zoom in more closely to unpick the characters' motivations and the plot in more detail. Figure 9 starts by breaking down the R&D effort by the broad therapeutic areas which Pharmaprojects uses. It seems that cancer has once again received a disproportionate boost from the overall pipeline expansion rate. With 8,480 drugs now in development for oncology, it has grown its footprint by 9.1%. With this, it returns to leader of the pack, overtaking the biotechnology group (which isn't really a therapeutic area, but it is currently included in this taxonomy). Cancer's rate of increase far outstrips those of the following group of therapeutic areas of neurologicals (up 4.6%), alimentary/metabolics (up 4.7%), and anti-infectives (up a paltry 2.0%).

Figure 9: **The R&D pipeline by therapeutic area, 2022 and 2023**

Source: Pharmaprojects®, January 2023



The increased oncological focus means that cancer continues to grab a greater share of the paragraphs. Now, 39.8% of all drugs are in development against some form of cancer, up again on last year's percentage, and continuing its steady march towards world domination. It does mean that, as it occupies more and more of the narrative, other therapeutic areas must be being squeezed proportionately (see Figure 10).

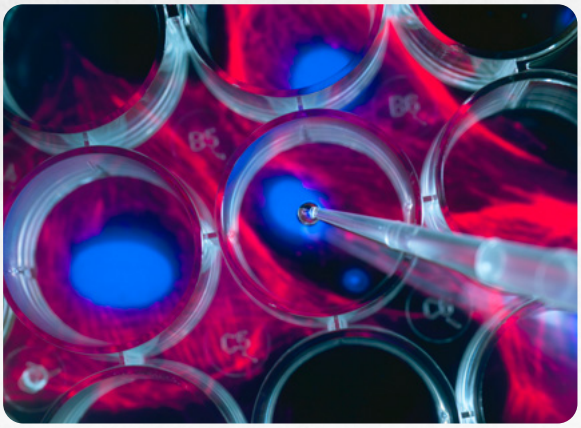
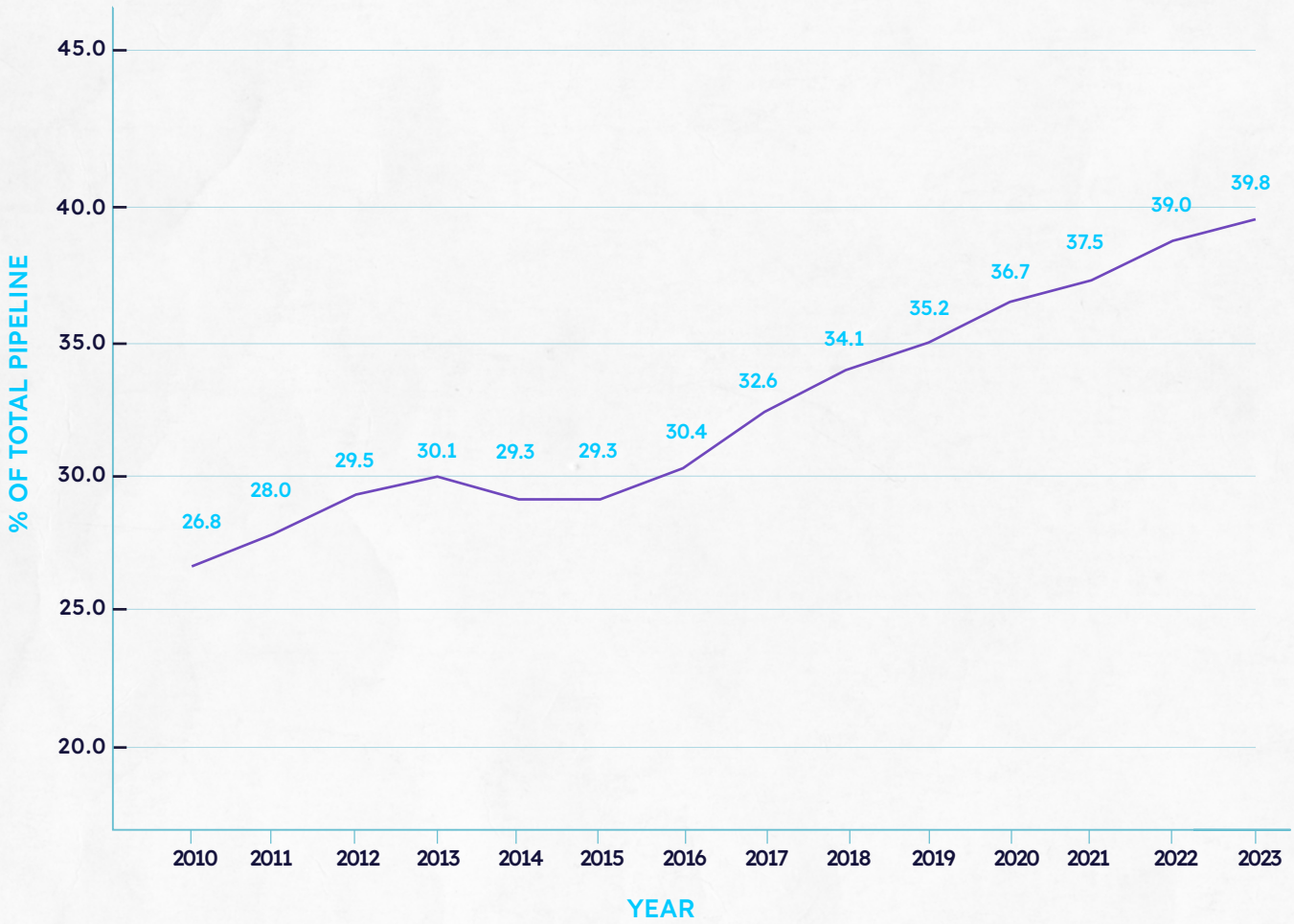


Figure 10: **Proportion of the pipeline which is in development for cancer, 2010–23**

Source: Pharmaprojects®, January 2023



Sharpening our focus somewhat, we move to Table 4, which lists the top 25 of the 243 individual therapeutic categories used to classify drugs in the Citeline suite of products. The anticancer, immunological category again commands the most attention, growing its pipeline size by 5.1%, but the more general anticancer category in second position trumped that figure, posting a massive 14.8% boost. Gene therapy once again came in third, although its rate of expansion has dramatically slowed, being up 6.3% as opposed to the 23.3% increase we saw in the previous 12 months. Elsewhere in the top 10, the status quo largely remains, although there are some sizeable rises in the numbers for immunosuppressants and CAR-T therapeutics at the lower end. Again, the most remarkable thing about this year's top 25 is how stable it is compared to the previous year. There are no new entries at all this year. This is one chapter in our story that's not exactly packed with incident.

TABLE 4: **Top 25 therapeutic categories**

Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	THERAPY	NO. OF ACTIVE COMPOUNDS 2023 (2022)	TREND
1 (1)	Anticancer, immunological	4,492 (4,275)	↑
2 (2)	Anticancer, other	3,622 (3,154)	↑↑
3 (3)	Gene therapy	2,083 (1,960)	↔
4 (4)	Monoclonal antibody, other	1,395 (1,277)	↔
5 (7)	Prophylactic vaccine, anti-infective	1,064 (983)	↔
6 (6)	Neurological	1,045 (993)	↔
7 (8)	Ophthalmological, other	984 (953)	↔
8 (5)	Antiviral, other	983 (998)	↔
9 (12)	Immunosuppressant	797 (713)	↑
10 (10)	Cellular therapy, chimaeric antigen receptor	792 (720)	↑
11 (11)	Antidiabetic	747 (717)	↔
12 (9)	Anti-inflammatory	722 (726)	↔
13 (14)	GI inflammatory/bowel disorders	705 (645)	↔
14 (13)	Musculoskeletal	677 (656)	↔
15 (16)	Cognition enhancer	641 (600)	↔
16 (17)	Respiratory	632 (596)	↔
17 (15)	Monoclonal antibody, humanized	624 (602)	↔
18 (18)	Cardiovascular	599 (595)	↔
19 (20)	Neuroprotective	595 (569)	↔
20 (19)	Hepatoprotective	594 (573)	↔
21 (21)	Dermatological	559 (504)	↑
22 (24)	Urological	519 (485)	↔
23 (25)	Analgesic, other	517 (484)	↔
24 (22)	Antiparkinsonian	516 (489)	↔
25 (23)	Monoclonal antibody, human	498 (488)	↔

As noted, cell and gene therapy continue to be major focuses for the industry. Figure 11 illustrates how they have both emerged as major drivers of drug development over the past 20 years. It's also worth noting that these two approaches form something of a Venn diagram. While there are 2,083 gene therapies and 2,049 cell therapies in development, 1,197 therapeutics are classified as both. These are therapeutics where cells are removed from the body and undergo genetic manipulation ex vivo before being reintroduced into the patient, with examples including the aforementioned CAR-T therapies. This means that we are reporting the development of 886 gene therapies which don't have a cell therapy component — these will be mostly the more traditional in vivo gene therapies, whereby attempts are made to correct genetic diseases by inserting a functional gene into the body instead. Similarly, there must be 852 cell therapies where no genetic manipulation is involved.

Figure 11: **The ongoing rise of gene and cell therapy, 1995–2023**

Source: Pharmaprojects®, January 2023

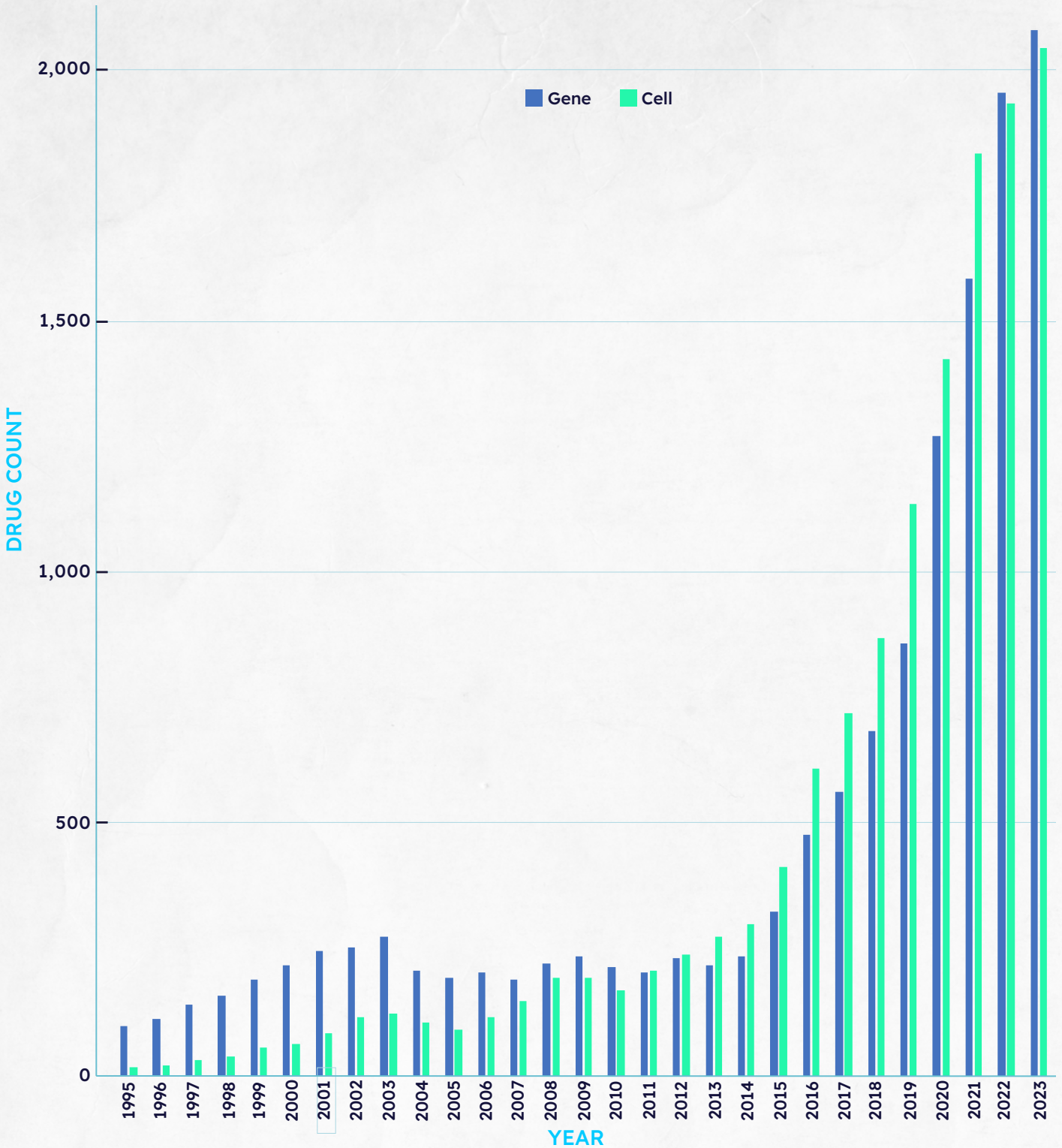
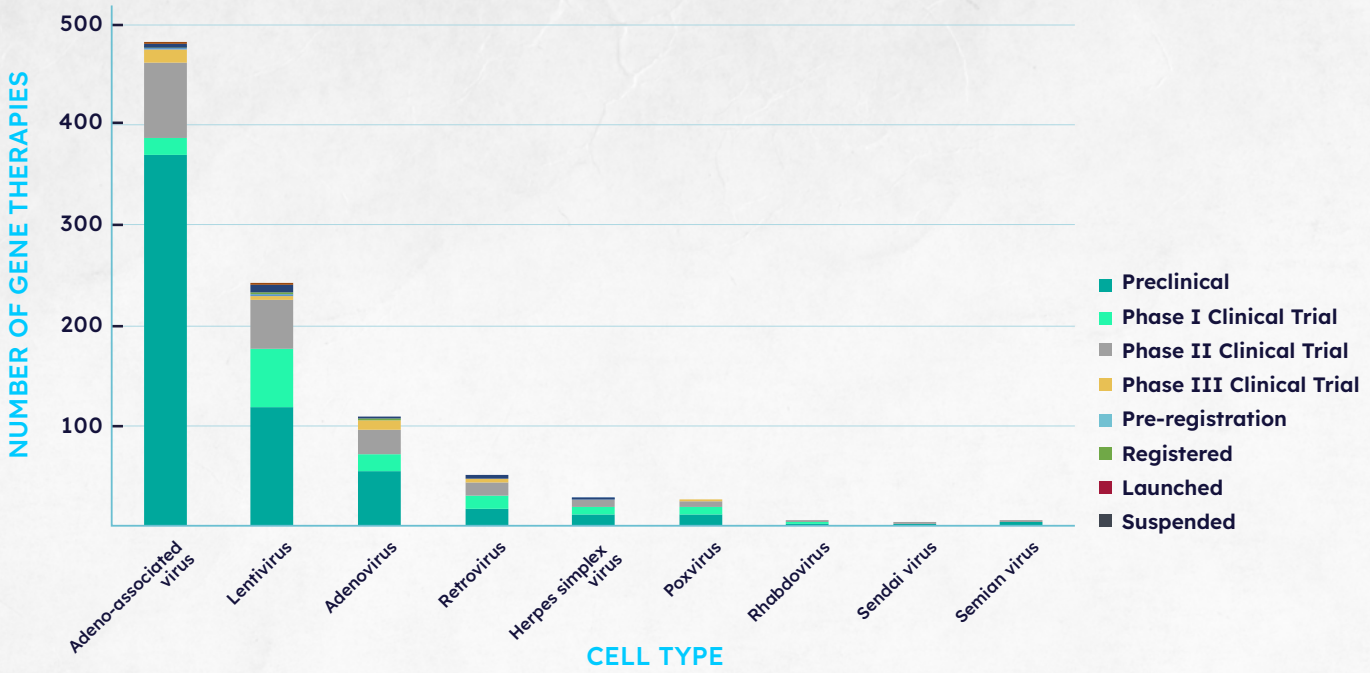


Figure 12: **Viral vectors used in gene therapy**

Source: Pharmaprojects®, January 2023



The viral vectors used in gene therapy also reflect the different ways this technique is used. Figure 12 shows that the adeno-associated viral vectors are the most popular, and it is this virus which is most commonly used for the in vivo gene therapeutics. There are slightly more under development this year (483 vs. 466). As the graph also breaks down each vector by phase of development, you can see that, although the vast majority are still in preclinical development, there are a sizeable number beyond that, especially at Phase II clinical trials. The second most common vector type, lentiviruses, in contrast are more usually used in the ex vivo transfection of cells for those agents which fall into both the gene therapy and cell therapy buckets. Their overall numbers fell over the past year, sitting at 241, down from 279. Numbers in the other categories haven't changed all that much year-on-year.

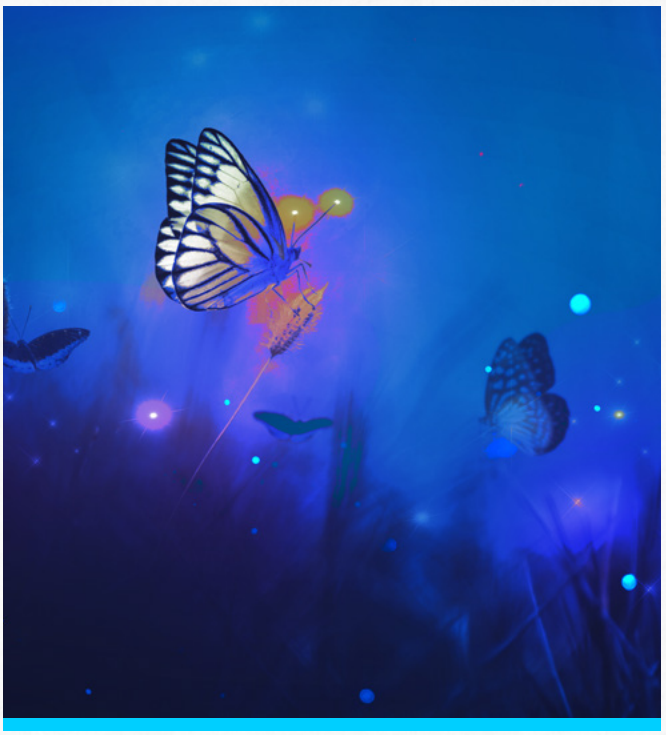


Figure 13: **Cell types used in cell therapies**

Source: Pharmaprojects®, January 2023

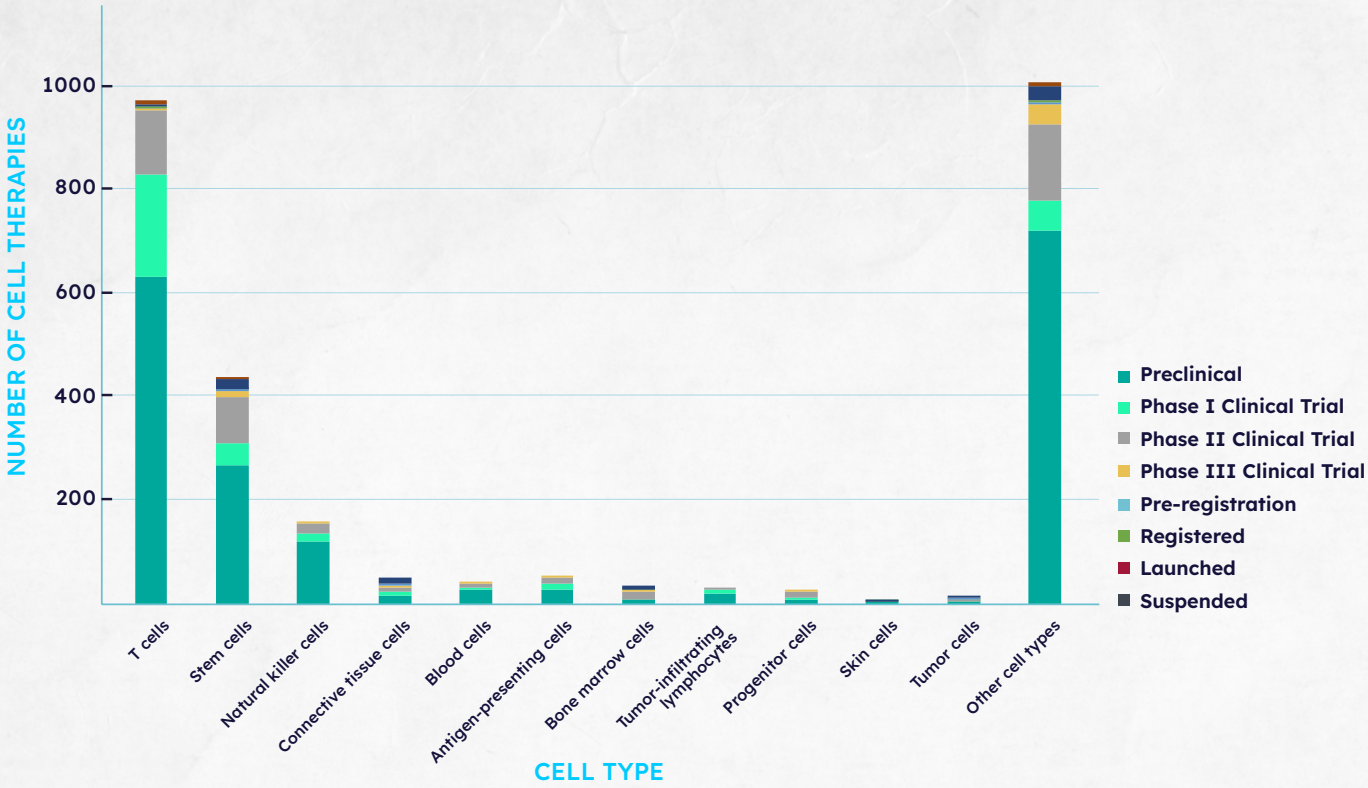


Figure 13 looks at the different types of cells being used in cell therapies. T-cells, such as those used in CAR-T therapeutics, are the most popular, with their overall number increasing this year from 909 to 976. Following behind are stem cells, which reported a slight drop from 448 to 437. What's notable about the cell therapy field is the huge array of different types of cells being utilized or investigated as potential therapeutics. The graph shows a large bar for "other cell types," which includes no fewer than 19 other cell types, indicating the diversity of approaches in use here.

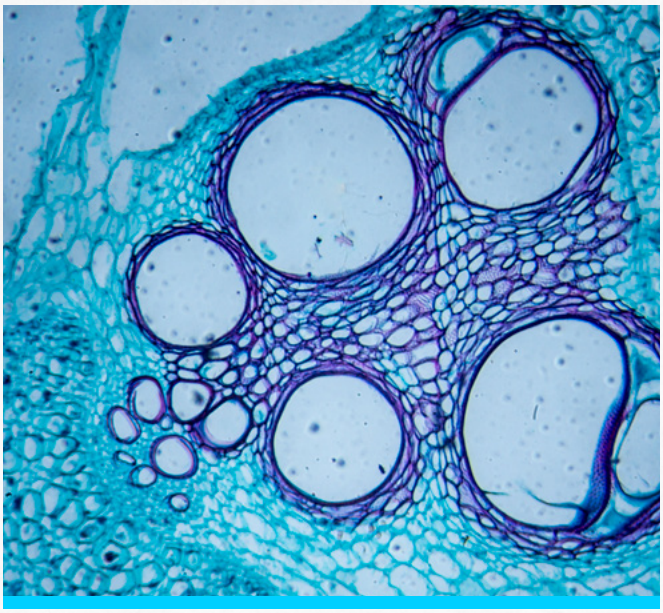


TABLE 5: **Top 25 diseases/indications**

Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	Drug disease	Number of drugs 2023 (2022)	TREND
1 (1)	Cancer, breast	965 (888)	↑
2 (2)	Cancer, lung, non-small cell	925 (832)	↑↑
3 (4)	Cancer, colorectal	741 (663)	↑
4 (5)	Cancer, pancreatic	675 (591)	↑↑
5 (3)	Infection, coronavirus, novel coronavirus	653 (677)	↔
6 (6)	Cancer, ovarian	587 (530)	↑
7 (9)	Cancer, brain	539 (485)	↑
8 (8)	Alzheimer's disease	529 (496)	↔
9 (7)	Cancer, prostate	523 (509)	↔
10 (10)	Cancer, leukemia, acute myelogenous	484 (462)	↔
11 (12)	Cancer, melanoma	476 (437)	↑
12 (11)	Diabetes, Type 2	475 (445)	↔
13 (19)	Cancer, gastrointestinal, stomach	449 (373)	↑↑
14 (14)	Cancer, myeloma	445 (431)	↔
15 (16)	Cancer, liver	444 (407)	↔
16 (13)	Infection, coronavirus, novel coronavirus prophylaxis	444 (436)	↔
17 (15)	Arthritis, rheumatoid	431 (427)	↔
18 (17)	Cancer, head and neck	408 (377)	↑
19 (18)	Parkinson's disease	407 (377)	↑
20 (20)	Cancer, lymphoma, non-Hodgkin's	399 (373)	↔
21 (21)	Non-alcoholic steatohepatitis	369 (360)	↔
22 (23)	Psoriasis	337 (328)	↔
23 (22)	COVID-19 complications	322 (332)	↔
24 (24)	Cancer, renal	281 (254)	↑
25 (25)	Asthma	258 (252)	↔

We're now zooming in to really examine in detail the specific motivators for the pharma industry at the individual disease level. Table 5 lists the top 25 diseases/indications (note that non-specific indications such as "Cancer, unspecified" have been removed from this analysis). Breast cancer remains the most popular target for novel drug R&D, with a hefty 8.7% increase in the number of candidates currently under study, but non-small cell lung cancer at number two has closed the gap with an even more impressive 11.2% expansion. Two more types of tumor come in next, both shuffling up a place, also evidencing increased interest: colorectal cancer (up 11.8%), and pancreatic cancer (up the most of the four, by 14.2%). Sliding down the top five is the category for therapeutics against COVID-19, which is down two places to fifth, and is the only disease in the top 25 to have fewer drugs in development this year than last year — but more on this in a minute. The novel coronavirus is joined in the top 10 by Alzheimer's disease at number eight as the only other non-cancer indication in the top 10. Indeed, 15 of the top 25 diseases are once again forms of cancer. Alzheimer's disease doesn't seem to have had the turbocharged boost in interest that the admittedly not entirely successful launch of Aduhelm (aducanumab) might have been expected to bestow on the sector. Its pipeline size only grew by 6.7%, only slightly above the average. Perhaps it will get a bigger shot in the arm now the marginally more impressive Leqembi (lecanemab) has also received approval.

Further down the chart, the most significant shift is a big rise for GIST, or gastrointestinal stomach cancer, picking up a 20.4% uptick — over a fifth more candidates now than in 2022. This contrasts with much of the rest of the table, which again is characterized by having exactly the same cast as last year, and with few significant changes.

This is the global picture, much like the English-language version of our novel, but just as most literary hits are translated into other languages, it can be instructive to look at versions of the top diseases chart across different parts of the world. Table 6 is quite revealing here. It shows that, across most of the world, non-small cell lung cancer has claimed the top spot, pushing breast cancer into second. It is only in Africa, where NSCLC doesn't even figure in the top eight, that breast cancer is top. COVID-19 is still the third biggest priority in the US and is runner-up in Africa, but it doesn't figure at all elsewhere. Similarly, rheumatoid arthritis features in the top four for Africa, Europe (both EU and non-EU), and South America, but is absent elsewhere. This table amply illustrates how, despite the global nature of the pharmaceutical industry, regional differences still play an important part.

TABLE 6: **Regional variations in R&D, by disease**

Source: Pharmaprojects®, January 2023

POSITION/ REGION	1	2	3	4	5	6	7	8
AFRICA	Cancer, breast	Infection, coronavirus, novel coronavirus	Diabetes, Type 2	Arthritis, rheumatoid	Infection, HIV/AIDS	Infection, coronavirus, novel coronavirus prophylaxis	Infection, tuberculosis	Infection, HIV prophylaxis
ASIA	Cancer, lung, non-small cell	Cancer, breast	Diabetes, Type 2	Cancer, gastrointestinal, stomach	Cancer, liver	Cancer, pancreatic	Cancer, lymphoma, non-Hodgkin's	Cancer, myeloma
CANADA	Cancer, lung, non-small cell	Cancer, breast	Cancer, prostate	Cancer, ovarian	Cancer, leukemia, acute myelogenous	Cancer, myeloma	Cancer, lymphoma, non-Hodgkin's	Amyotrophic lateral sclerosis
CHINA	Cancer, lung, non-small cell	Cancer, breast	Cancer, gastrointestinal, stomach	Cancer, lymphoma, non-Hodgkin's	Cancer, liver	Cancer, myeloma	Cancer, pancreatic	Cancer, leukemia, acute myelogenous
EU	Cancer, lung, non-small cell	Cancer, breast	Arthritis, rheumatoid	Cancer, ovarian	Cancer, myeloma	Cancer, lymphoma, non-Hodgkin's	Cancer, gastrointestinal, stomach	Cancer, renal
EUROPE, NON-EU	Cancer, lung, non-small cell	Cancer, breast	Arthritis, rheumatoid	Cancer, ovarian	Diabetes, Type 2	Cancer, lymphoma, non-Hodgkin's	Cancer, myeloma	Cancer, gastrointestinal, stomach
JAPAN	Cancer, lung, non-small cell	Cancer, breast	Cancer, lymphoma, non-Hodgkin's	Cancer, gastrointestinal, stomach	Cancer, pancreatic	Cancer, liver	Cancer, leukemia, acute myelogenous	Cancer, myeloma
OCEANIA	Cancer, lung, non-small cell	Cancer, breast	Cancer, colorectal	Cancer, ovarian	Cancer, pancreatic	Cancer, myeloma	Cancer, lymphoma, non-Hodgkin's	Cancer, leukemia, acute myelogenous
SOUTH AMERICA	Cancer, lung, non-small cell	Cancer, breast	Arthritis, rheumatoid	Diabetes, Type 2	Cancer, gastrointestinal, stomach	Asthma	Cancer, prostate	Cancer, renal
UK	Cancer, lung, non-small cell	Cancer, breast	Cancer, colorectal	Cancer, ovarian	Cancer, lymphoma, non-Hodgkin's	Cancer, gastrointestinal, stomach	Cancer, renal	Cancer, leukemia, acute myelogenous
USA	Cancer, lung, non-small cell	Cancer, breast	Infection, coronavirus, novel coronavirus	Cancer, pancreatic	Cancer, leukemia, acute myelogenous	Cancer, ovarian	Cancer, myeloma	Cancer, lymphoma, non-Hodgkin's

KEY

Cancer	Musculoskeletal	Infectious Disease
Alimentary/Metabolic	Respiratory	CNS

One recurring trope which many books feature is the anti-hero. Anti-heroes are characterized by qualities usually considered to be dark or villainous, but with traits that sometimes blur the moral lines, forcing us into an uneasy fascination with them. Examples include Scarlett O'Hara in Margaret Mitchell's *Gone with the Wind* (1936), Pinkie Brown in Graham Greene's *Brighton Rock* (1938), Michael Corleone in Mario Puzo's *The Godfather* (1969), or, at the extreme end, Patrick Bateman in Bret Easton Ellis's *American Psycho* (1991). Even though clearly infected with evil, these characters are propulsive forces in the narrative. Such has been the case in pharma with COVID-19. It has wreaked a terrible toll, but out of the wreckage, some good has come, as it has accelerated vaccine research and changed clinical trial practices forever.

As I noted earlier, I'm hoping that I can kill off my separate analyses on the virus after this year, sending the disease off to be lost among the huge array of background characters. But how close is COVID-19 to becoming "just another disease"? After all, 12 months ago, its latest sequel, Omicron, was becoming a bestseller. Figure 14 does suggest that R&D efforts against the killer virus did settle down in 2022 to something approaching a steady state. The number of newly identified antivirals, prophylactics, and drugs to treat its complications definitely tailed off further during 2022 compared to 2021, seemingly across the board. Barring a further unexpected plot twist, it is to be hoped that three years in a starring role were enough, and its relegation to the chorus is imminent.

FIGURE 14: **COVID-19 response in years one, two, and three of the pandemic**

Source: Pharmaprojects®, January 2023

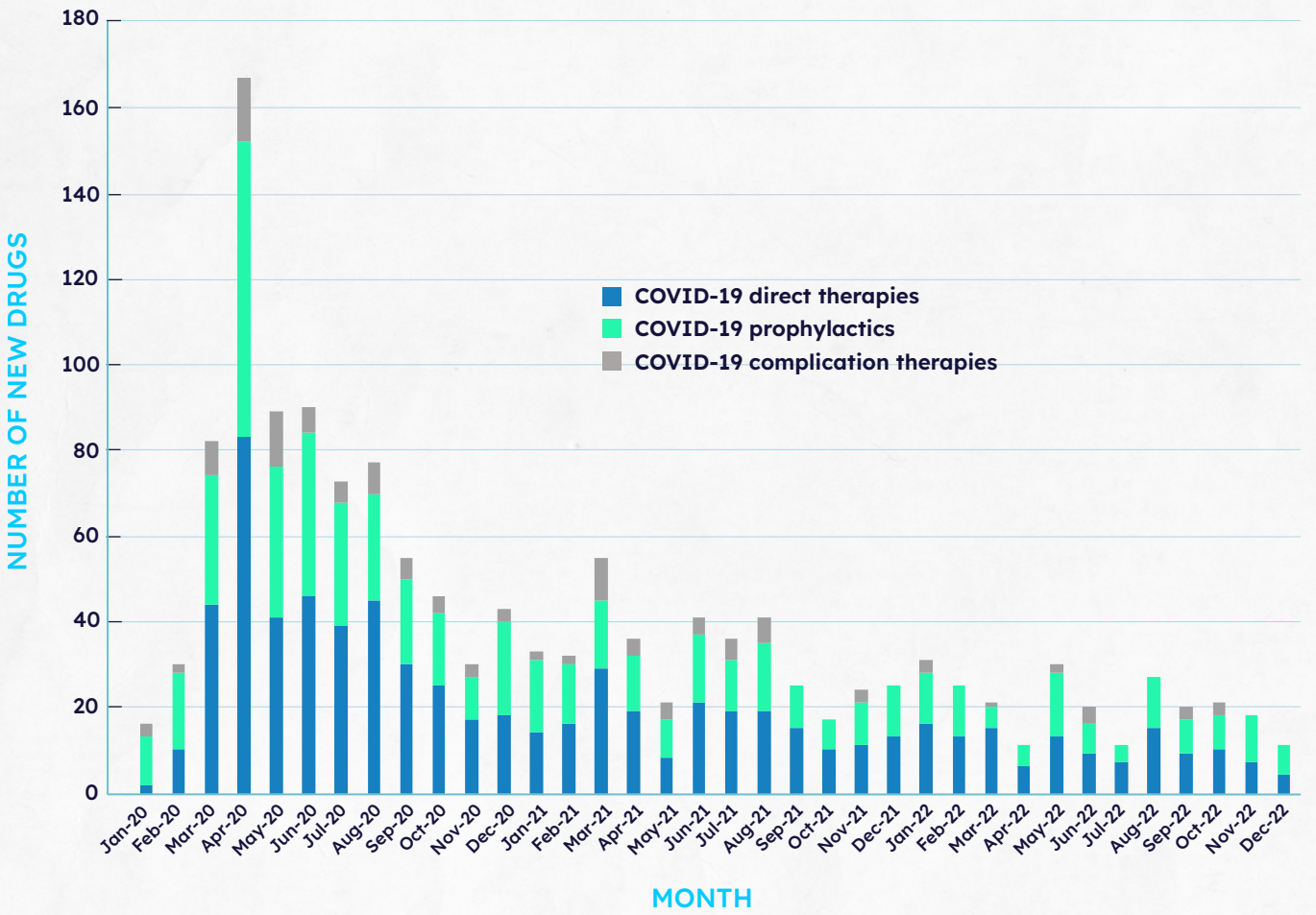
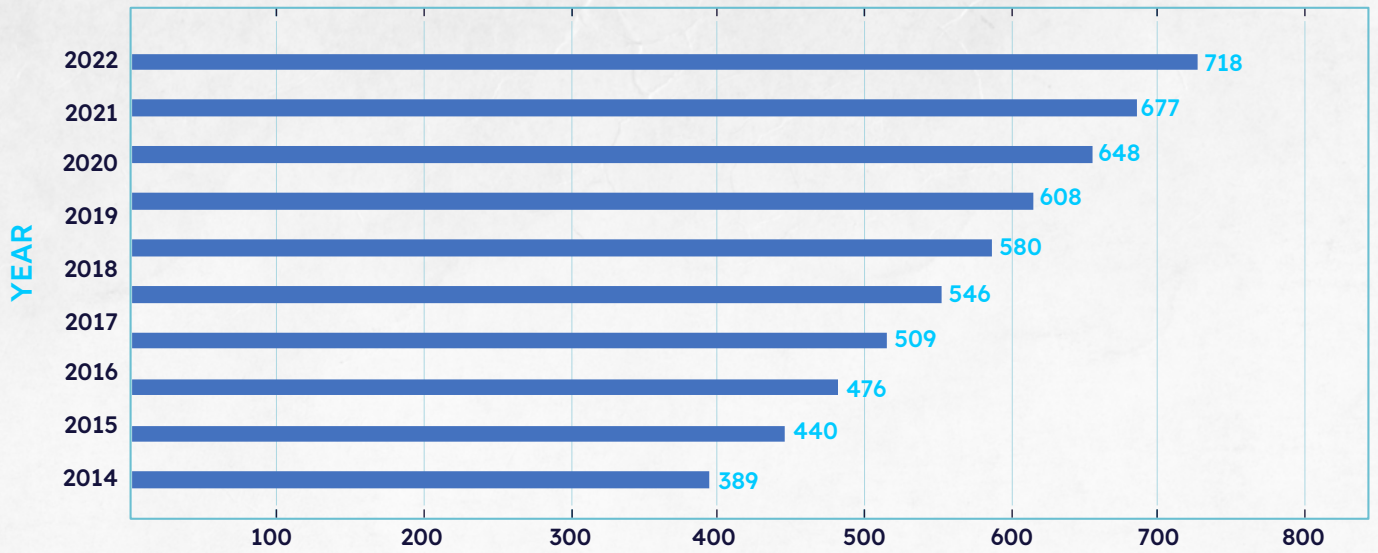


FIGURE 15: **Number of rare diseases being targeted by pharma, 2014–22**

Source: Pharmaprojects®, January 2023

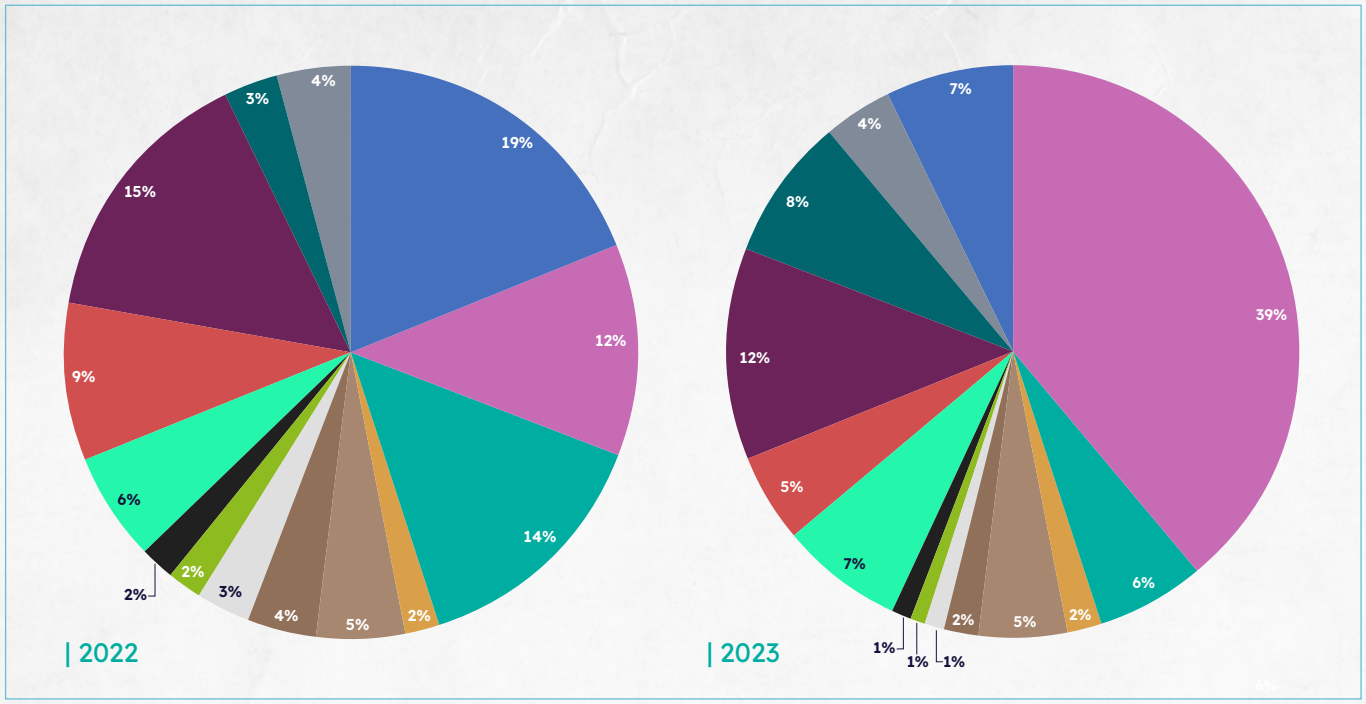


NUMBER OF RARE DISEASES BEING TARGETED BY R&D

While some diseases have unfairly hogged the limelight, others can appear to be mere footnotes to the overarching narrative, but taken as a whole, form an important part of the story. Such is the case with rare diseases. Individually, they may not take up many pages, but taken together, they are forming an increasingly vital part of the story. In Pharmaprojects, a rare disease is defined as one with a prevalence of less than 1 in 2,000 people in the EU, or affecting fewer than 200,000 people in the US (equivalent to around 1 in 1,600 people). As Figure 15 shows, 2022 saw even more rare indications meriting a mention, with 718 individual orphan indications now being the focus of at least one drug development project.

FIGURE 16: **Rare diseases by therapeutic area, by number of diseases and number of drugs, 2022 and 2023**

Source: Pharmaprojects®, January 2023

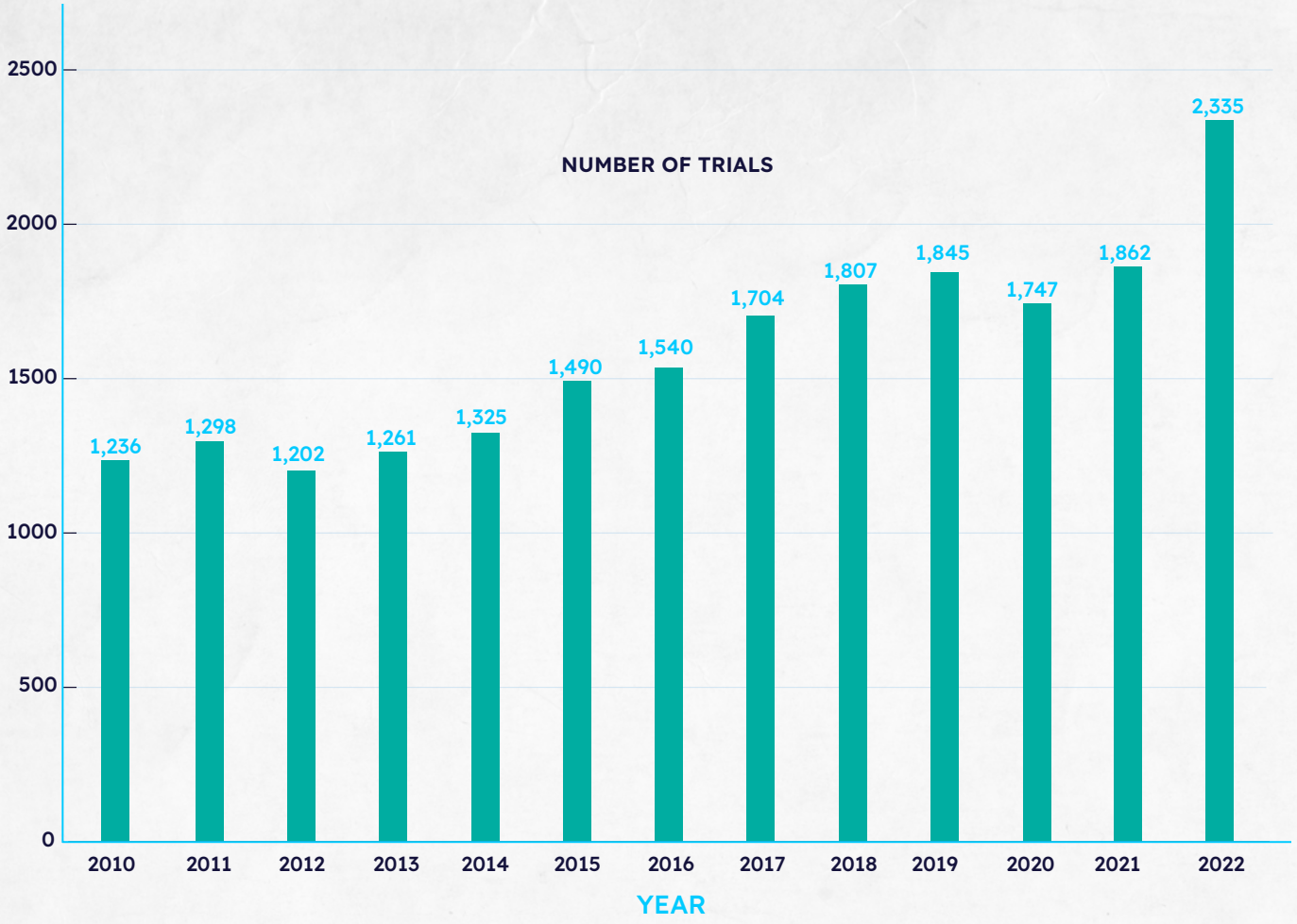


All of this rolls up to a total of 6,682 drugs being currently in development against at least one rare disease, which represents 31.4% of all drugs, up from 6,080 (30.2%) 12 months ago. While rare diseases can fall into any therapeutic area, their distribution by therapeutic area is at considerable variance compared to where the focus of rare disease R&D actually sits. Figure 16 shows that the highest proportion of rare diseases, 19%, are classified as alimentary/metabolic.

But when it comes down to the number of drugs in development, only 7% of the rare disease total falls into the alimentary/metabolic bucket, indicating that there are a lot of rare diseases here with few drugs in development for each. Given that a lot of niche genetic disorders affecting metabolism fit into this category, this is probably what you would expect. In contrast, while cancer only accounts for 12% of rare diseases — fourth by percentage — it still grabs the largest slice of pie by far in terms of drugs, with 39%.

FIGURE 17: **Industry-sponsored rare disease trials by start date, 2010–22**

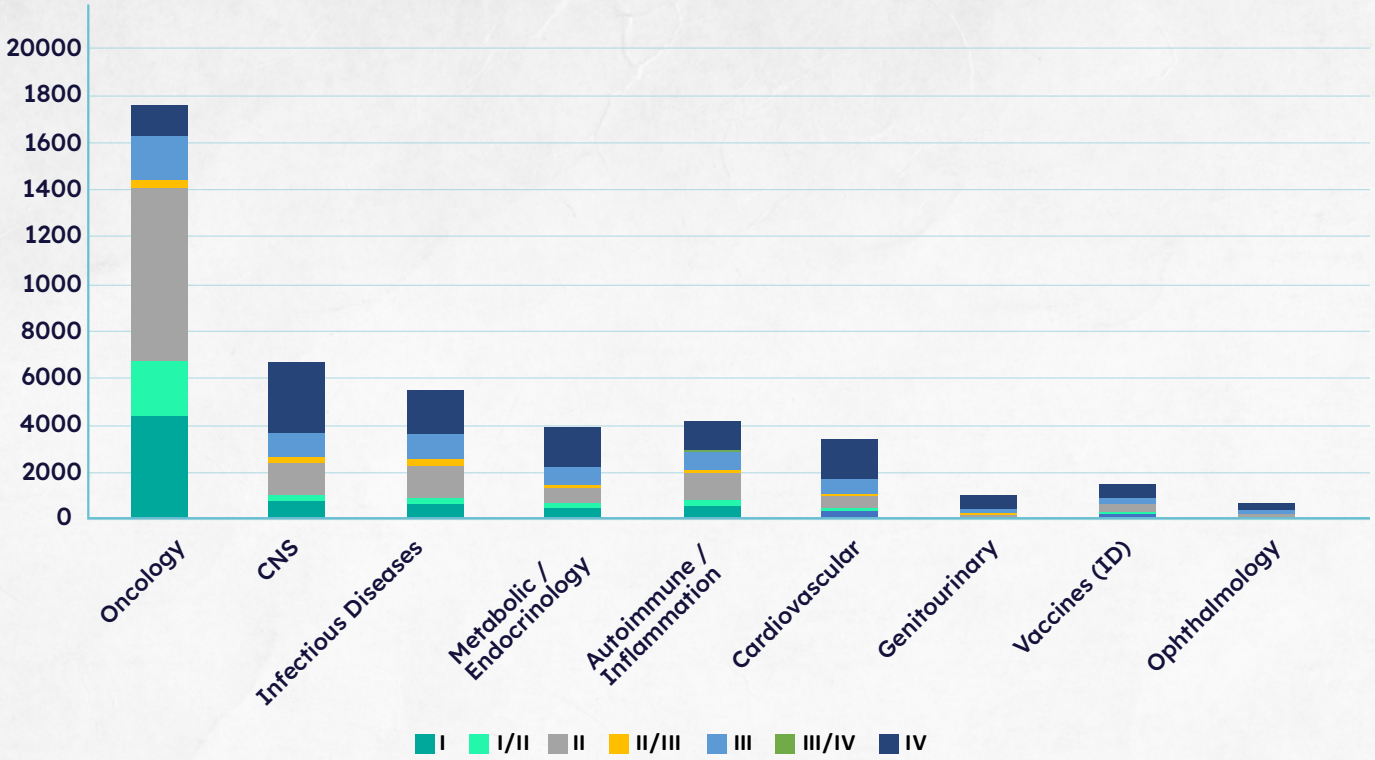
Source: Trialtrove®, January 2023



This increasing focus on rare diseases is emphasized by looking at our sister product Trialtrove and examining how many trials starting last year were in rare conditions. You can see from Figure 17 that there was quite an uptick in trial starts during 2022 — a rise of 25.4%. While it's true that Trialtrove has expanded its rare disease coverage over the past year, this alone cannot account for such an increase. Andrew Benson, senior director for Trialtrove, estimates the coverage expansion would only lead to a percentage increase in the single digits. And, of course, this data chimes with our own observation that rare disease R&D continues to be on the rise.

FIGURE 18: **Ongoing clinical trials, by therapeutic area**

Source: Trialtrove®, January 2023



Moving away from rare diseases but sticking with clinical trials, Figure 18 shows the full panoply of clinical trials under way at the start of 2023 by therapeutic area, as reported by Trialtrove (note that Trialtrove uses slightly different therapeutic areas to Pharmaprojects). In the world of trials, cancer pretty much has one ring to rule them all, with almost three times as many ongoing (open, closed, or temporarily closed trials at Phases I–IV) clinical trials as any other therapeutic area. The number's up too, from 16,207 to 17,614, indicating that there are 8.7% more oncology trials under way this year than last. CNS comes in second with an even more impressive 10.0% uptick. While nearly all therapeutic areas reported an increase, there was one notable exception: anti-infectives. There are actually 1.2% fewer anti-infective trials under way this year — the strongest indication yet that the COVID bubble, which had fueled significant increases in the previous two years, has finally begun to burst. Indeed, the number of ongoing trials involving treatments, vaccines, or supportive therapies for the novel coronavirus is down from over 2,500 to 2,384 this year, while the number of planned trials, although still high for a single disease, also seems to have peaked, falling from 1,770 in 2022 to 1,679 now, as I predicted it would this time last year.

FIGURE 19: **Numbers of drugs receiving orphan drug status, expedited review designation*, and emergency authorization**, 2013–22**

Source: Pharmaprojects®, January 2023

• Data for 2013 not complete as we only began systematically recording the dates of these events mid-year
• Emergency Authorizations only tracked from 2019

While the overall structure of the pharmaceutical industry is little changed in 2023, it is still encouraging to see drugs in development for more diseases overall (1,452 individual indications now have drugs under development, up from 1,408 a year ago) and for more rare diseases too — plenty to retain the interest of all our company characters. As the distraction of COVID begins to fade, organizations both big and small can return to their areas of expertise with enhanced perspectives and renewed confidence in their abilities to develop novel therapeutics in a timely manner.

"And now that you don't have to be perfect, you can be good"

John Steinbeck, *East of Eden* (1952)

In literature, there is a technique known as deus ex machina, whereby, once the story has got to a place where the protagonists are seemingly in an impossible position, something unexpected occurs to help resolve the issue and engineer an unlikely happy ending. Famous examples include the resolutions to both H.G. Wells's *The War of the Worlds* (1898) and William Golding's *The Lord of the Flies* (1954). While medicine generally relies more on slow and steady progress, sometimes there are "happy accidents" or sudden great leaps forward which can change the direction of pharma R&D quite abruptly. It might not quite qualify as a deus ex machina, but the leap into immuno-oncology is probably the biggest handbrake turn which the industry has made this century. The idea that the body's own immune system could be trained to fight cancer was quite revolutionary 20 years ago. Within a very short time, it has become one of the dominant forces in pharma R&D.

TABLE 7: **Top 25 mechanisms of action (pharmacologies)**

Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	Drug disease	Number of drugs 2023 (2022)	% at PR, R, or L	TREND
1 (1)	Immuno-oncology therapy	3,393 (3,307)	2.2	↔
2 (2)	Immunostimulant	1,472 (1,494)	9.2	↔
3 (4)	T-cell stimulant	1,091 (1,061)	1.1	↔
4 (5)	Immune checkpoint inhibitor	618 (575)	5.0	↔
5 (3)	Gene expression inhibitor	283 (280)	1.8	↔
6 (6)	Genome editing	274 (280)	0	↔
7 (9)	Protein degrader	221 (197)	0.9	↑
8 (8)	CD3 agonist	198 (196)	2.5	↔
9 (7)	Radiopharmaceutical	192 (183)	9.4	↔
10 (10)	Angiogenesis inhibitor	192 (198)	24	↔
11 (12)	Natural killer cell stimulant	186 (160)	0	↑
12 (11)	PD-L1 antagonist	181 (165)	4.4	↔
13 (19)	Immunosuppressant	179 (173)	36.3	↔
14 (14)	PD-1 antagonist	152 (143)	11.8	↔
15 (16)	Immune checkpoint stimulant	150 (145)	0	↔
16 (13)	Vascular endothelial growth factor (VEGF) receptor antagonist	142 (146)	21.1	↔
17 (15)	Microbiome modulator, live microorganisms	128 (115)	0	↔
18 (17)	Glucagon-like peptide 1 receptor agonist	111 (111)	6.3	↔
19 (18)	Apoptosis stimulant	103 (105)	15.5	↔
20 (20)	ErbB-2 antagonist	97 (91)	15.5	↔
21 (21)	K-Ras inhibitor	87 (73)	2.3	↑
22 (23)	Microbiome modulator	83 (65)	1.2	↑
23 (22)	Surface glycoprotein (SARS-CoV-2) antagonist	83 (84)	10.8	↔
24 (24)	DNA inhibitor	82 (79)	29.3	↔
25 (25)	Cyclooxygenase 2 inhibitor	71 (71)	19.7	↔

ABBREVIATIONS	R: registered
PR: pre-registration	L: launched

In our Table 7, which lists the top 25 mechanisms of action, immuno-oncology has this year become even more pre-eminent. Firstly, to be clear, our mechanism classification is hierarchical, and is therefore skewed to favor broader terms. This is because, with over half of the pipeline still at the preclinical phase where often full mechanistic information is unknown or undisclosed, there tend to be a lot of drugs where only a broad mechanism class can be ascribed. As drugs move up through development stages, these general categorizations are often replaced by something more precise. There are also a number of "umbrella" terms, which are created to permit searching for our subscribers across mechanisms in certain broader categories. The immuno-oncology (IO) category is one such of these and is applied to drugs in the IO class even if more specific mechanistic information can also be ascribed, so that all IO drugs can be found in a single search. This is one of the reasons that it is applied to so many drugs.

Nevertheless, the amount of drug R&D under way which uses this still relatively new approach is remarkable. With 3,393 IO drugs in development at the start of 2023, fully 15.9%, or almost one-sixth, of all drugs are using this technique. This number is only up by 2.6% this year, but probably the more interesting percentage is the one to the right of the number of drugs column in this table: the percentage of drugs using this strategy which have made it to the later stages (pre-registration, registered, or launched) of development. With just 2.2% of projects getting this far, the vast majority of IO drugs are still very much at the earlier stages. This represents a huge leap of faith into the world of IO. Many of these drugs will fail, but the industry clearly has huge belief in the potential of this strategy.

Some more specific IO strategies also make strong showings in the top 25. T-cell stimulants, natural killer cell stimulants, and both immune checkpoint inhibitors and stimulants are among other broader IO-related categories in the table, whereas some specific IO techniques have also made their presence felt, such as CD3 agonists, PD-L1 antagonists, and PD-1 antagonists. All are showing increased pipeline sizes, although only natural killer cell stimulants are posting a significant increase this year.

Overall, this is another table exhibiting little change from last year, with the trend line in the final column being flat for a large number of categories. Notable exceptions include protein degraders, microbiome modulators, and K-Ras inhibitors, all of which showed above average increases. The middle of these is one of two entries joining the top 25, with the other being the return of COX-2 inhibitors at number 25. But do take a minute to note how many of the top mechanisms have as yet 0% of their drugs in the later stages of development; the industry is certainly embarking on a fair few blind dates here.

TABLE 8: **Top 25 drug protein targets**

Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	Target	Number of drugs 2023 (2022)	TREND
1 (2)	CD274 molecule **(PD-L1)**	210 (194)	↔
2 (1)	CD3 epsilon subunit of T-cell receptor complex	207 (199)	↔
3 (4)	CD19 molecule	194 (174)	↑
4 (3)	erb-b2 receptor tyrosine kinase 2 **(Her2)**	187 (177)	↔
5 (5)	epidermal growth factor receptor	178 (161)	↑
6 (6)	programmed cell death 1 **(PD-1)**	165 (159)	↔
7 (7)	vascular endothelial growth factor A	160 (158)	↔
8 (8)	glucagon-like peptide 1 receptor	126 (116)	↔
9 (17)	KRAS proto-oncogene, GTPase **(K-Ras)**	118 (87)	↑↑
10 (10)	5-hydroxytryptamine receptor 2A	117 (103)	↔
11 (9)	opioid receptor mu 1	107 (104)	↔
12 (14)	insulin receptor	87 (90)	↔
13 (13)	TNF receptor superfamily member 17 **(BCMA)**	87 (91)	↔
14 (16)	cannabinoid receptor 1	86 (87)	↔
15 (15)	tumor necrosis factor	86 (90)	↔
16 (22)	TNF receptor superfamily member 9 **(CD137)**	84 (70)	↑
17 (11)	nuclear receptor subfamily 3 group C member 1 **(glucocorticoid receptor)**	83 (96)	↓
18 (18)	membrane spanning 4-domains A1 **(CD20)**	82 (83)	↔
19 (19)	opioid receptor kappa 1	80 (79)	↔
20 (12)	surface glycoprotein, SARS coronavirus 2	78 (91)	↓
21 (38)	claudin 18	75 (49)	↑↑
22 (25)	androgen receptor	74 (64)	↑
23 (29)	transforming growth factor beta 1	74 (62)	↑
24 (21)	CD47 molecule	73 (70)	↔
25 (20)	prostaglandin-endoperoxide synthase 2	73 (75)	↔

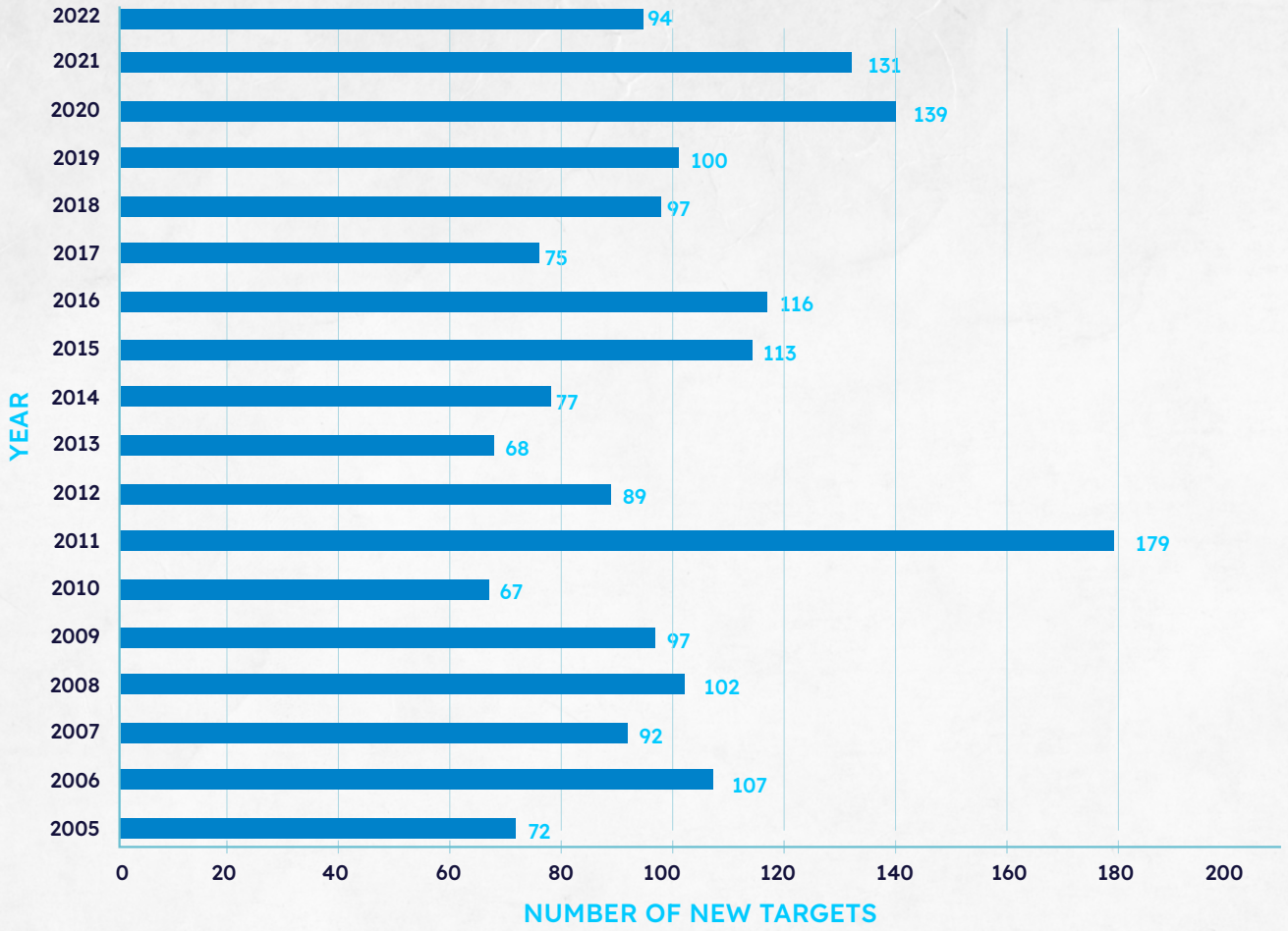
Note: NCBI names are used, except for additions in bold made by us for clarity.

There's more to engage the reader's interest in Table 8, which presents the top 25 protein targets which drugs in development right now are hitting. Each of the targets in our classification has entries in the NCBI's Gene database, which covers the gene that encodes each protein. Here, we actually have a new number one. The CD274 molecule, better known as PD-L1, now becomes the most targeted protein in all of drug development, further illustrating the meteoric rise of IO to dominance. It deposes the CD3e molecule, a cornerstone in the development of bispecific antibodies, which spent just one year at the summit. Its predecessor at the top spot, Her2, slips a further place to number four, allowing another IO-related target, CD19, to enter the top three. This is a target used in a large number of CAR-T cell therapies.

Eight of the top 10 targets, including the entire top seven, are proteins targeted in the treatment of cancer. One of these, K-Ras, makes a dramatic entry into the top 10, with a 24.1% increase in the number of its candidates. But it is another novel cancer target which makes the most significant advance:

FIGURE 20: **Number of new drug protein targets identified by Pharmaprojects, by year, 2005–2022**

Source: Pharmaprojects®, January 2023



claudin 18, crashing into the higher echelons on the back of a phenomenal 53.1% increase in drugs hitting it. Claudin 18's isoform 2 is commonly found in gastric cancers such as GIST, so it is a new hot target for drugs against these tumor types. Elsewhere, there's a climb for another IO target, CD137, and a return to the top 25 for the more traditional transforming growth factor beta 1. Slipping down the chart is a very old target, in the shape of the glucocorticoid receptor, and a newer one in the COVID-19 spike protein, which falls to number 20, in the most compelling evidence yet that we are past peak coronavirus. Overall, there are lots of shifting narratives to follow within the world of drug targets.

However, 2022 was less than stellar in terms of the number of drug targets which were newly identified. Only 94 targets had drugs in development against them for the first time — the lowest number for five years (Figure 20). This also brings 2022 in as a slightly below average year for innovation, with the mean for the past 18 years coming in at 101. But this number doesn't seem to be following a particular trend, and could be just a rebound following on from two very good years. And there are more targets currently being hit by drugs in active development than there were this time last year, with 1,974, up from 1,952 12 months ago, so I don't think that there should be any particular cause for concern here.

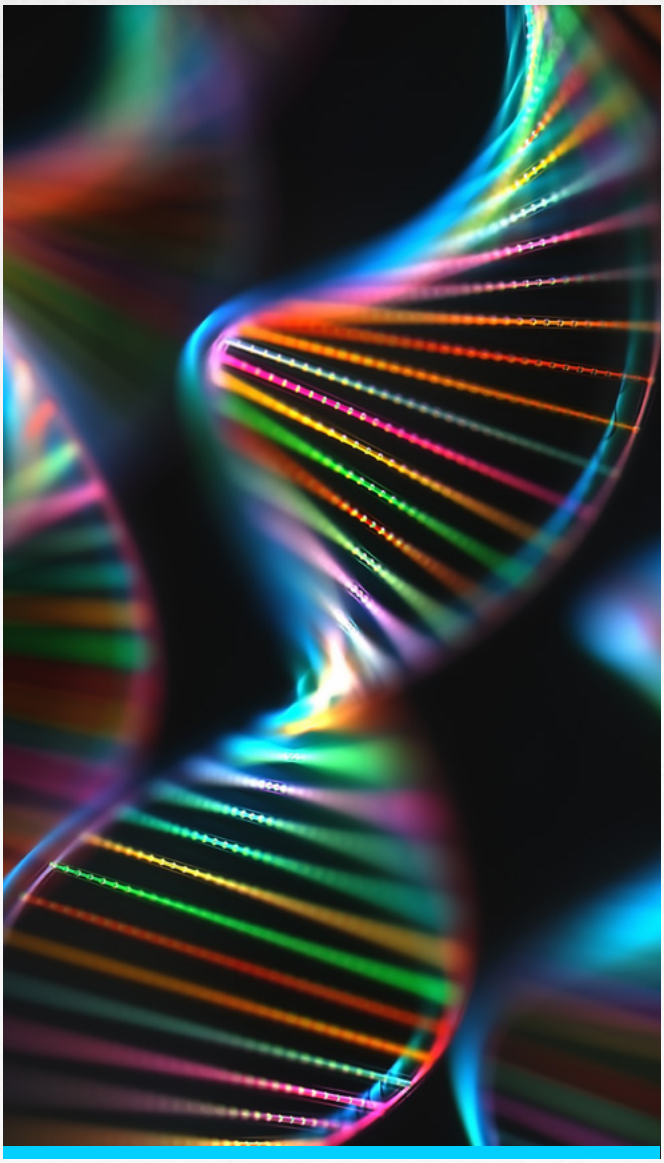
"Reshaping life!

People who can say that have
never understood a thing about life — they have never felt its breath, its heartbeat — however much they have seen or done. They look on it as a lump of raw material that needs to be processed by them, to be ennobled by their touch.

But life is never a material, a substance to be molded. If you want to know, life is the principle of self-renewal, it is constantly renewing and remaking and changing and transfiguring itself, it is infinitely beyond your or my obtuse theories about it"

(Boris Pasternak, *Doctor Zhivago* (1957)

Our final set of data looks at the types of drugs in current development and the technologies used to produce them. This might be considered the equivalent of a drug's modus operandi — a term used in literature (and elsewhere) to describe a method or procedure which is commonly employed. In fiction, it's most commonly used in the crime genre, where it's often shortened to MO. Famous examples where our hero detective must work out the killer's MO to solve the crime include Thomas Harris's *The Silence of the Lambs* (1988) and pretty much every Sherlock Holmes novel by Sir Arthur Conan Doyle.



While not suggesting for a second that the pharma industry's MO has any equivalence with fictional killers, it's instructive to look at the techniques which it is employing to produce the drugs that are under development. Table 9 breaks down the pipeline by what we call the drugs' origins — the types of molecules classified by how they are made. This is another hierarchical classification, so, like the mechanism of action classification, the more general categories prosper in cases of early development where information is scant and more specific data is not yet available. Also, in this classification, there is not an "Unknown" option, so where no information is available, drugs are assigned to "Chemical, synthetic" by default, flattering its figures somewhat. Nevertheless, the "Chemical, synthetic" class — basically your classical small molecule drug — is most definitely still the most popular MO for the pharma industry. It tops the chart by some distance, with a 7.8% increase in its numbers this year. Clearly, the traditional way of making a molecule is very much alive and well.

TABLE 9: **Top 25 origins of pipeline drugs**

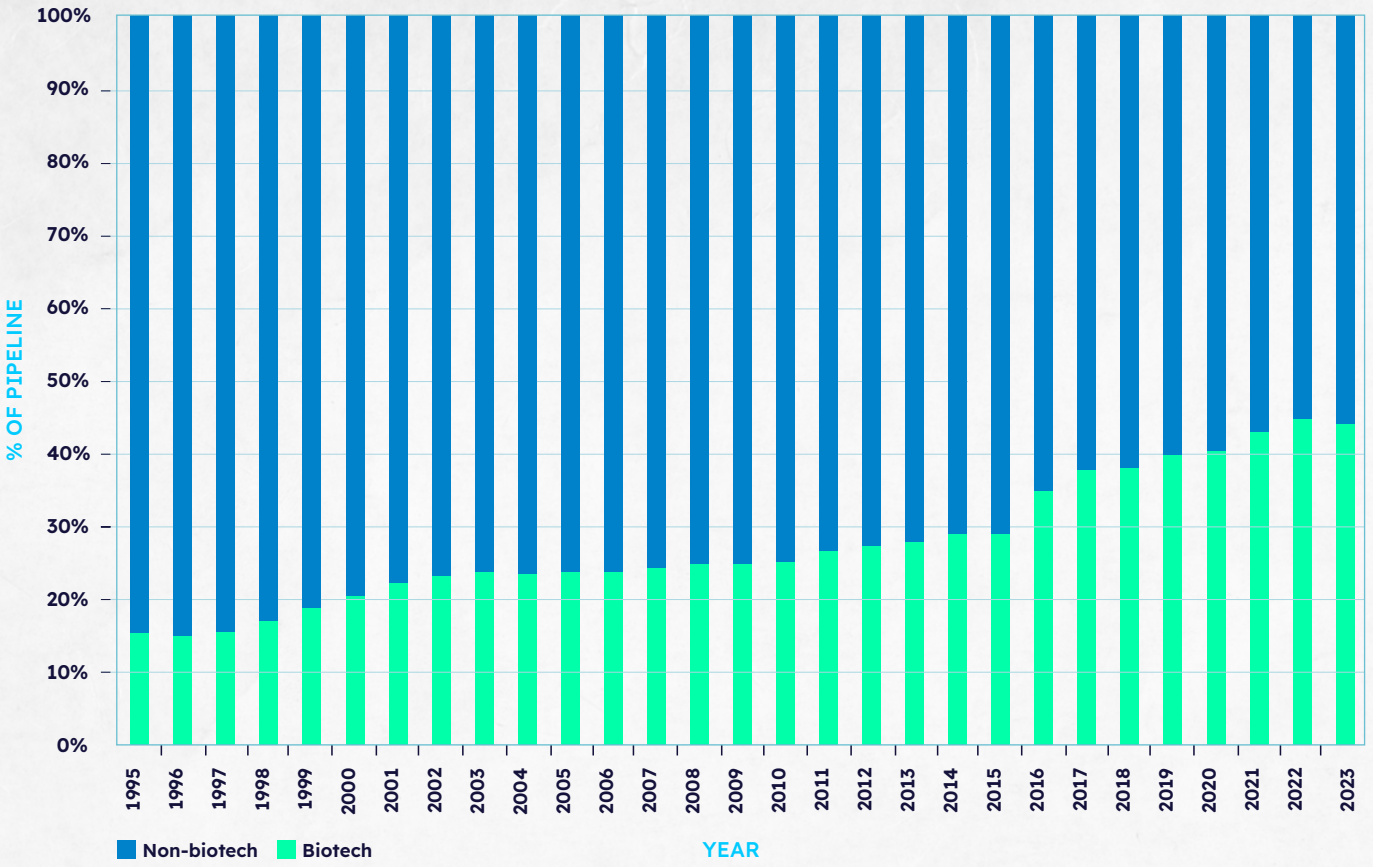
Source: Pharmaprojects®, January 2023

POSITION 2023 (2022)	Origin	Number of drugs 2023 (2022)	TREND
1 (1)	Chemical, synthetic	10,307 (9,565)	↑
2 (2)	Biological, protein, antibody	2,734 (2,681)	↔
3 (4)	Biological, protein, recombinant	932 (865)	↔
4 (5)	Biological, cellular, autologous	758 (776)	↔
5 (3)	Biological, cellular, heterologous	687 (587)	↑
6 (6)	Biological, nucleic acid, viral vector	677 (680)	↔
7 (9)	Biological, cellular	583 (558)	↔
8 (8)	Chemical, synthetic, nucleic acid	536 (489)	↑
9 (7)	Biological, virus particles	534 (493)	↑
10 (10)	Biological, protein	523 (541)	↔
11 (12)	Biological, nucleic acid	477 (471)	↔
12 (11)	Chemical, synthetic, peptide	461 (453)	↔
13 (19)	Biological, other	358 (237)	↑↑
14 (14)	Biological, bacterial cells	330 (283)	↑
15 (16)	Biological, peptide	254 (272)	↔
16 (13)	Natural product, plant	215 (215)	↔
17 (15)	Biological, nucleic acid, non-viral vector	185 (184)	↔
18 (17)	Biological, peptide, recombinant	171 (171)	↔
19 (18)	Biological	164 (187)	↓
20 (20)	Chemical, semisynthetic	57 (53)	↔
21 (21)	Natural product, fungal	51 (46)	↔
22 (23)	Natural product, bacterial	50 (55)	↔
23 (22)	Natural product	38 (41)	↔
24 (24)	Natural product, animal	22 (23)	↔
25 (25)	Chemical, synthetic, isomeric	21 (24)	↔

Antibodies remain the second most popular type of drugs, followed by recombinant proteins, although these two categories' advance on the summit has slowed this year. The categories which are posting the most significant increases in the top 10 this year are heterologous cell therapies, synthetic nucleic acids, and viruses, the latter of which covers a broad range of both therapeutic lytic viruses and virus-based vaccines.

FIGURE 21: **Biological vs. non-biological drugs as a percentage of the pipeline, 1995–2023**

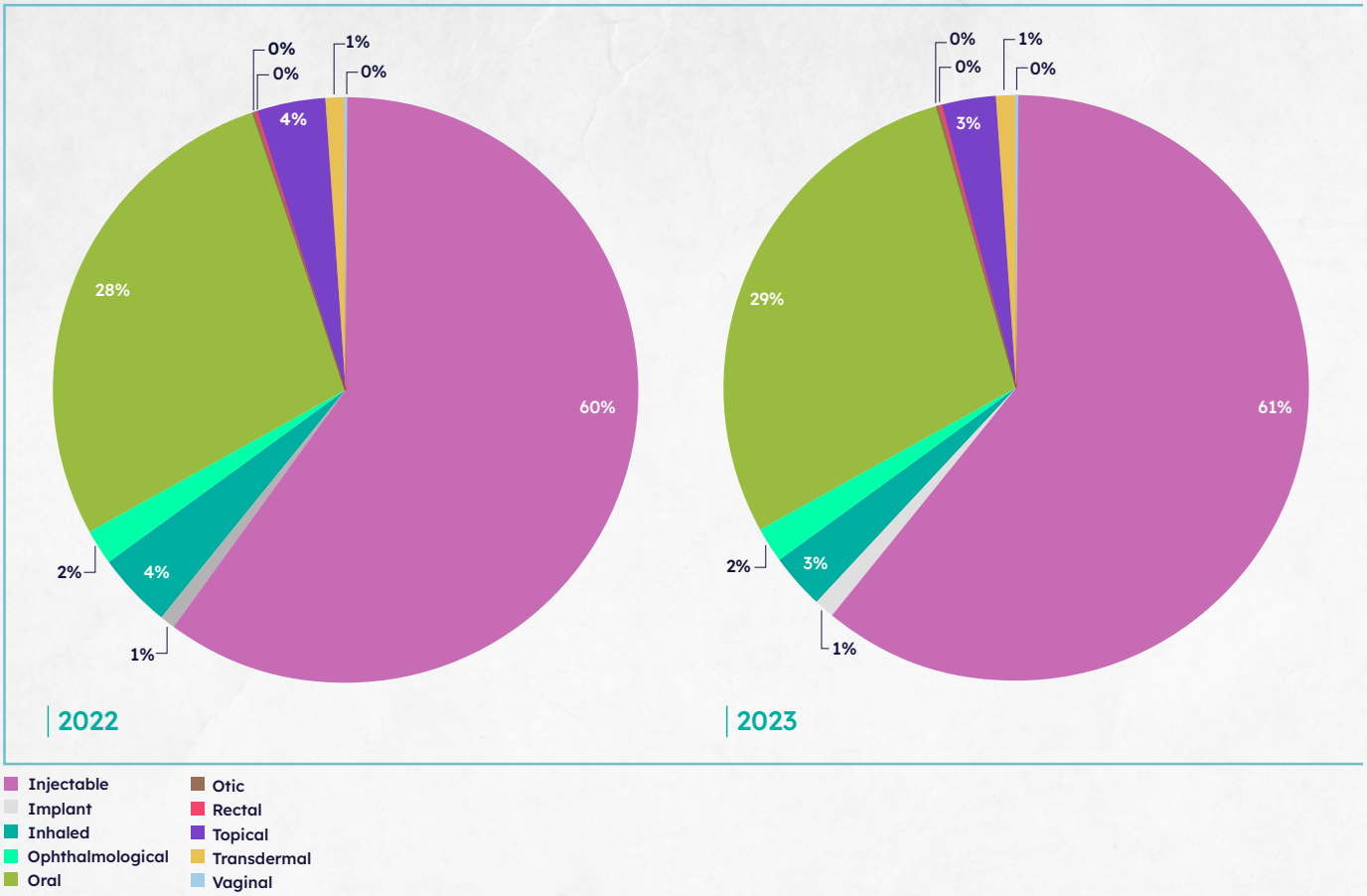
Source: Pharmaprojects®, January 2023



With biotechnology-based drugs commanding a lot of attention, it's interesting to take a broader view of drugs as a whole by biotech vs. non-biotech. It's tempting to think that the industry is gradually moving away from small molecules, and as Figure 21 shows, this has largely been the case over the past three decades — but not this year. For the first time since 2004, there is a slightly smaller percentage of biotech-derived drugs in the pipeline than there were the previous year. The proportion is now 44.0%, down from 44.7%. It's impossible to say yet whether this is the start of biotech and chemical settling at an equilibrium, or whether this is just a blip in biotech's continued advance. This is a metric where next year's sequel should be a particularly interesting read.

FIGURE 22: **Pipeline by delivery route, 2022 and 2023**

Source: Pharmaprojects®, January 2023



The slight clawback by chemical drugs is reflected in this year's statistics of the pipeline by delivery route (Figure 22), where the percentage of drugs delivered by the oral route has increased from 28% to 29%. But there is also a concomitant 1% increase in injectables, the route most biotech-based drugs use. Losing out is the inhalation delivery route — as a method of delivering proteins, this route has disappointed in recent years, as a failure to deliver consistent enough plasma concentrations has stymied many projects in this area.

"I must be taken as I have been made. The success is not mine, the failure is not mine, but the two together make me"

Charles Dickens, *Great Expectations* (1861)

Epilogue: Where Next for the Pharma Saga?
Could global events send the industry off topic?

We are coming to the end of the story of pharmaceutical R&D for 2023. The ongoing saga inevitably has many loose threads which we will pick up on again in the ineluctable sequels in subsequent years. But like many a good literary novel does, let's try to tie a few things up in an epilogue. We can also speculate here as to what might happen to our characters in future volumes.

After the seismic events of the past few years, 2022–23 appears to have been a period where pharma settled down to very much business as usual. There really isn't a strong storyline to latch on to this year; as our analyses have shown, it was a period striking for its stability and lack of change. If you wanted to sum up the year with a one-sentence review, you could probably say: "There was a bit more of pretty much everything," and leave it there. Overarching trends and surprising plot twists have been thin on the ground — probably no bad thing after the Grand Guignol of the pandemic. Not every novel needs to be a Mary Shelley-like gothic horror — sometimes blander fare can be just the comfort read you need.

This is partly due to the fact that, although it hasn't gone away, the threat of COVID-19 does seem to have finally been defanged, ex-China at least. In Western countries, although the virus still produces new waves of infection, our immune systems are now largely primed by a combination of broad vaccine uptake and past infection (the number of people who seem to have completely escaped at least one bout of infection is dwindling away to nothing). We've pretty much reached the fabled herd immunity. You can add to this the fact that management of serious disease has come on leaps and bounds from the experience garnered over the past three years. As a result, in the UK at least, where I'm writing from, COVID rarely makes the news anymore — the story has moved on. The disease is well on its way to becoming just another one of the plethora of seasonal respiratory viruses which are a nuisance but hardly impact our daily lives. Let's not forget that, as I was writing this report last year, the Omicron variant was sweeping the world, and we were wondering whether this would ever end.

We are not entirely out of the woods yet though, with the deteriorating situation in China at the time of writing still having the potential to throw a wrench in the works. As the ruling Communist party suddenly and unexpectedly abandoned its controversial and ultimately untenable "Zero-COVID" policy from December 2022 onwards, the country has been hit by waves of infection. Cities have fared particularly badly, with Beijing being poleaxed first, and at one time it was estimated that 80% of China's population was affected, causing many parts of the country to run out of analgesics and similar cold and flu remedies. At the time of writing (mid-January 2023), it was looking like COVID-related death rates in the country may be peaking, but with vaccine uptake and quality in the country so low, there are likely to be subsequent waves, especially with the peak travel period of Chinese New Year imminent. While it doesn't necessarily follow that high levels of virus in the population make the emergence of a new, more dangerous variant more likely, this is still not beyond the realms of possibility, a fact that must cast something of a shadow over a world which is enjoying being in the sunny uplands of a supposedly post-COVID world.

The way that China has handled the pandemic has had broader consequences for its own pharmaceutical industry, and by extension also for the global pharma R&D community. Domestic confidence remains low, with the prospects of an improvement in the investor environment in the near term thought to be slim. The country has also gone through another round of drug price cuts in its annual review, further jangling the nerves of the industry. Meanwhile, some Chinese companies filing US NDAs on the back of China-only trials have found the FDA to be not as receptive as they might have hoped. This is all occurring in the context of generally worsening Sino-American relations. And in the background always lurks the issue of Taiwan, and whether China might now feel emboldened to make a move on the disputed territory.

Epilogue: Where Next for the Pharma Saga?
Could global events send the industry off topic?

Something which undoubtedly upped the ante on this last year was Putin's decision to invade and wage war on Ukraine. Quite apart from ratcheting up East-West tensions, the prolonged conflict has affected pharma R&D in a multiplicity of ways. It further destabilized supply chains still wobbling from COVID-initiated disruptions, and has impacted global contract research organizations that conduct clinical trials there and in the surrounding region. And, of course, it has further exacerbated already volatile energy prices, pushing up costs for everyone, including the ever energy-hungry pharmaceutical industry, further fueling inflationary pressures on an already struggling global economy. Against this background of multiple destabilizing events in 2022, it's a wonder that the pharma R&D pipeline remained as stoutly anchored as it was across the year.

Let's turn our attention to what may or may not happen in 2023, as we indulge ourselves in a bout of speculative fiction. Speculative fiction is a literary genre which includes situations or topics not recognizable in the real world, and can include science fiction, fantasy, or dystopian novels. While it can often involve wild ideas, one of its functions is to comment on current trends, often serving as an allegorical warning to the world on how things might pan out if unchecked. Famous examples include Aldous Huxley's *Brave New World* (1932), Anthony Burgess's *A Clockwork Orange* (1962), and Philip K. Dick's *Do Androids Dream of Electric Sheep?* (1968). While we don't wish to indulge in flights of fancy too untethered from reality here, a little near-term crystal ball gazing always piques the reader's interest.

The big unknown, as it approaches its unwelcome first anniversary, is the war in Ukraine. With no sign as yet of anything like a peace deal, it may come down to a military conclusion, with some analysts believing that a Ukrainian victory could come as early as this spring. Others are more gloomy, expecting the conflict to drag on, possibly up until Putin's grip on power weakens. A worst-case scenario is further escalation, but the likelihood of this does seem to have receded. A spring end would obviously be the best option for the global economy and the pharmaceutical industry, allowing both to fully emerge finally from the shadow of COVID.

The other great uncertainty, as intimated earlier, is whether the pandemic is really over, and if we can move to treating COVID as just another seasonal disease. With China such a major source of active ingredients and manufacturing for the sector, the emergence of COVID-19 massively disrupted supply chains even more than the Ukrainian war has done, and drove a move towards increased "onshoring." Some industry players are wary that the political temperature may rise further in the year ahead, leading to extra difficulties. Speaking to our sister publication Scrip, Michael Cruse, COO of Reneo Pharmaceuticals, speculated that: "Globally, we could see increased trade tensions with China and possibly India. I think every organization that is manufacturing or sourcing from these countries, and others, needs to be very aware of their supply chain and how they can mitigate disruptions should they occur." On the same lines, Susan Conroy, CEO of Therakind, commented: "Political instability and conflicts may limit access to drugs, excipients, processes and it may be overcome by operating multiple manufacturing facilities, having a robust distribution infrastructure, and putting greater emphasis on developing stable medicinal products that are easily transportable." Cathy O'Brien, VP for international sales at UPS Healthcare, noted that: "With the need to distribute billions of doses of COVID-19 vaccines we saw new and expanded supply chains built and tested in record time," but warns that, "the effort to re-shore may be more complicated than governments think."

Epilogue: Where Next for the Pharma Saga?
Could global events send the industry off topic?

Macroeconomic factors also threaten to make 2023's story more of a thriller than a work of poetry. With inflation running riot in many countries, and recession under way, additional interest rate rises might further push up pharma's costs. Many of the industry commentators quoted in Scrip have used the term "headwind," such as Teknova's CEO Stephen Gunstream, who stated: "The current market environments provide a strong headwind for biotech and pharma in 2023. Unfortunately, I believe this will limit investment in novel early-stage therapies, due to the desire to conserve capital in the first half of 2023." First Wave BioPharma CEO James Sapirstein concurred, noting that: "The investment climate could continue to be difficult, especially if interest rates rise." Pressure from rising costs could affect the pace of drug development, according to Jody Staggs, interim CEO of SWK Holdings, who predicted that: "Some life sciences companies are experiencing challenges with escalating costs from clinical trials, driven by inflation, difficulty staffing and challenges in recruiting patients. This can have a material impact on how drug and medical device makers advance their programs. Higher clinical trial costs add to a company or program's cash burn while skewing the revenue needed to justify funding certain programs." But opinion is split on whether things will get worse before they get better. In a survey carried out by our sister service Evaluate Vantage in early November 2022 among public and private investors, bankers, and other biopharma industry employees, 60% thought that the US biotech market had already bottomed out, but of those who thought it had further to fall, a quarter believed the nadir may not be hit until 2024 or beyond.

If rising costs and a difficult economic environment could lower investment and slow or halt certain R&D projects, what are the prospects like for deals in 2023? Another of our sister services, Biomedtracker, reported 2,600 pharma deals during 2022, including 1,340 financing deals. Both of these numbers were strikingly lower than their 2021 equivalents of 3,148 and 1,610, respectively. However, the tone of commentators seems notably optimistic for this year, with many hoping that the negative deal-making and funding environment might have bottomed out in 2022. Richard Wilson, senior vice president at Astellas Gene Therapies, told Scrip: "I'm expecting we might see an uptick in deal-making in 2023, as larger organizations think that the time is right to start making more moves." Andrew Harrow, a partner in Goodwin's life sciences group, concurred: "From an M&A perspective, we are expecting deal volume to increase in 2023 with corporate-led M&A leading the way," he said. "Biopharma valuations have fallen, both in the private and public markets, and pharma companies are still sitting on plenty of cash; further, the need to fill their product pipelines remains. All of this, and the fact that the capital markets are still probably not a viable alternative option for most companies, should lead to an increase in M&A activity across the market."

So, it's certainly not all doom and gloom, despite major disrupting forces in the world at large. As we reach the conclusion of our epic tale, like many a novelist whose work has been full of jeopardy, intrigue, and drama, we would like to provide something akin to a happy ending. The loose plot thread of just how successful 2022 ended up being for the industry will be tied up in the companion volume to this report, the NAS Supplement, which looks at those drugs whose stories reached a satisfying conclusion during the year, focusing as it does on all of the New Active Substances which made it to market for the first time during the course of the year. But our focus here is on the pipeline itself at the start of 2023, which, in a tale full of incident — war, pestilence, etc. — emerges at the end of our story in a pretty decent state. Like a character in a good novel, it has certainly been on a journey over the past few years, and is older and wiser, having learned a few life lessons along the way. The COVID-19 pandemic has certainly been one of the major drivers of narrative change, and has left lasting differences in the way in which the pharmaceutical industry conducts its business, and, in particular, its clinical trials. But, in many ways, these changes were not revolutionary and were under way already, and the pandemic merely accelerated change. Just as many businesses were already exploring hybrid working models, pharma was already looking at decentralized trials. Rather than ripping up the novel's first draft and starting again, COVID just hastened a few necessary rewrites.

Epilogue: Where Next for the Pharma Saga?
Could global events send the industry off topic?

The pharmaceutical industry enters 2023 admirably unperturbed by the events which have buffeted it. While hardly having sailed serenely through the storm, it hasn't ended up shipwrecked à la Daniel Defoe's *Robinson Crusoe* either. The take-home message from our magnum opus this year is that pharma R&D continues to grow pretty much across the board. There has been comparatively little year-on-year structural change in terms of the composition of the pipeline and its characters, just gentle – and therefore hopefully sustainable – growth. This is what pharma needs if it wants to continue to be *The Neverending Story* (Michael Ende, 1979).. The Pharmaprojects Pharma R&D Annual Review will be back again next year to critique the next chapter.

"I rarely end up where I was intending to go, but often I end up somewhere I needed to be"

Douglas Adams
The Long Dark Tea-Time of the Soul
(1988)

About the Author

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Ian Lloyd is the Senior Director of Pharmaprojects at Citeline, overseeing the content and analyst services for our drug development solution. He supports clients in their drug pipeline data requirements and inquiries, providing insight into the best search strategies to answer their drug-related business questions and also identifying and analyzing trends in pharma R&D. For the past 31 years, he has authored the “Pharma R&D Annual Review” and its new active substances (NAS) launches supplement. This has become a must-have industry report for those seeking to identify the changing fortunes of drug R&D. Ian joined Pharmaprojects in 1987, when it was part of PJB Publications. Prior to joining Citeline’s Pharmaprojects, Ian previously worked in molecular biology as a research assistant at the University of Bristol.

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