

Pharma R&D Review: What Changed In 2018, What To Look Out For In 2019

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Agenda

The drug R&D pipeline in 2019, and how it is changing

- Total pipeline size
- Success stories of 2018
- Top companies
- Leading therapies and diseases
- Mechanisms and targets
- Biotech vs pharma

The outlook for pharma for the year ahead

- Launches expected from 2018 drug approvals
- Drug approvals to look out for in 2019
- Macro issues likely to affect the industry

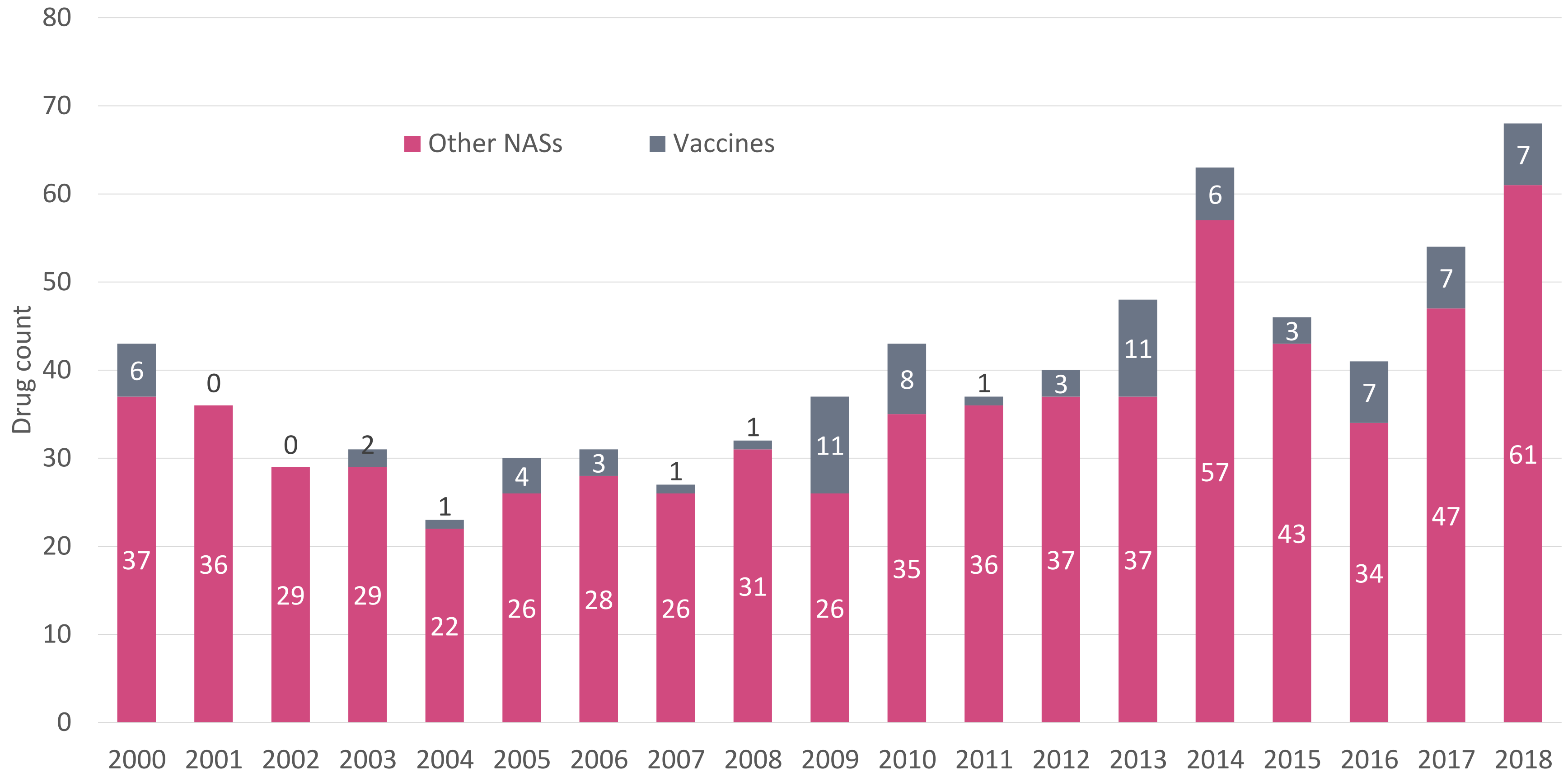
The total drug R&D pipeline in 2019

Total pipeline size has grown by 6%



Successes in 2018 – New active substance drug launches

2018 was the best year on record for New Active Substance launches



Novel new drug approvals/launches 2018 – Part 1



- **Vitrakvi** (larotrectinib) from Loxo/Bayer for solid tumors that have a NTRK gene fusion
 - First tissue-agnostic cancer therapy
- **Tibsovo** (ivosidenib) from Agios/CStone for acute myelogenous leukemia
 - The first isocitrate dehydrogenase 1 inhibitor to reach the market
- **Copiktra** (duvelisib) from Verastem chronic lymphocytic leukemia, small lymphocytic lymphoma and follicular lymphoma
 - A dual-acting PI3 kinase delta and gamma inhibitor
- **Yivyka** (polyinosinicpolycytidylic acid/inactivated virus) for advanced solid tumors
 - A new immunological approach to cancers launched in Cambodia

Novel new drug approvals/launches 2018 – Part 2



ALIMENTARY/METABOLIC

- **Crysvita** (burosumab) from Kyowa Hakko Kirin/Ultragenyx for X-linked hypophosphatemia
 - Inhibits fibroblast growth factor 23
- **Goofice** (elobixibat) from Ajinomoto/Mochida/EA Pharma for chronic constipation
 - An ileal bile acid transport inhibitor and sodium/bile acid cotransporter inhibitor
- **Lamzede** (velmanase alfa) from Chiesi for alpha-mannosidosis
 - Enzyme replacement therapy for alpha mannosidase II
- **Palynziq** (pegvaliase) from BioMarin for hyperphenylalaninemia
 - Pegylated phenylalanine ammonia lyase

Novel new drug approvals/launches 2018 – Part 3



ANTI-INFECTIVE

- **Trogarzo (ibalizumab)** from Theratechnologies for HIV infection
 - Humanized anti-CD4 MAb for heavily treatment-experienced adults
- **Xofluza (baloxavir marboxil)** from Shionogi/Roche for influenza
 - CAP-dependent endonuclease



OPHTHALMOLOGY

- **Luxturna (voretigene neparvovec)** from Spark/Novartis for RPE65 mutation-associated retinal dystrophy
 - First approved in vivo gene therapy in the US
- **Rhopressa (netarsudil)** from Aerie Pharmaceuticals for glaucoma
 - Rho-associated kinase 2 inhibitor

Novel new drug approvals/launches 2018 – Part 4



BLOOD & CLOTTING

- **Cablivi** (caplacizumab) from Ablynx for thrombotic thrombocytopenia purpura
 - A nanobody Factor VIII inhibitor
- **Tavalisse** (fostamatinib disodium) from Rigel for idiopathic thrombocytopenia purpura
 - Syk tyrosine kinase inhibitor



CNS/NEUROLOGICAL

- **Aimovig** (ereunumab) from Amgen/Novartis
- **Emgality** (galcanezumab) from Eli Lilly
- **Ajovy** (fremanezumab) from Teva
 - Calcitonin gene-related peptide inhibitors for migraine prophylaxis

Other selected new drug approvals/launches 2018



HONORABLE MENTIONS

- **Tegsedi** (inotersen) and **Onpattro** (patisiran) from Ionis/Akcea and Alnylam, respectively for transthyretin-related hereditary amyloidosis
 - Antisense and RNAi products for this rare disease
- **Epidiolex** (cannabidiol) from GW Research for Lennox-Gastaut syndrome and Dravet syndrome
 - Types of epilepsy – first for a cannabis-based product in the US
- **Three drugs for rare cancers**
 - **Xospata** (gliteritinib) from Kotobuki/Astellas for refractory acute myeloid leukemia
 - **Lumoxiti** (moxetumomab pasudotox) from AstraZeneca for hairy cell leukemia
 - **Azedra** (ultratracer iobenguane (I31)) from Molecular Insight for pheochromocytoma and paraganglioma

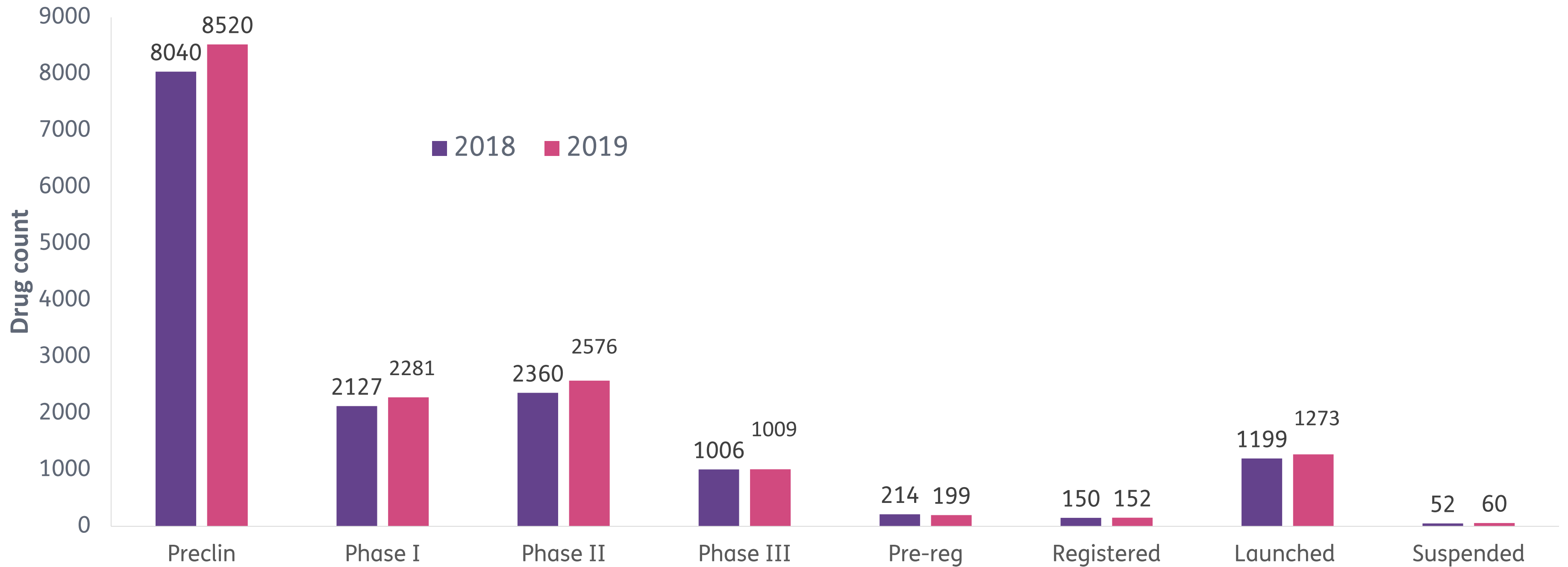
Most successful companies for drug launches in 2018

| Company | Number of NAS launches 2018 | Position by pipeline size |
|-------------------------|-----------------------------|---------------------------|
| Pfizer | 4 | 9 |
| Merck & Co | 4 | 8 |
| Eli Lilly | 2 | 10 |
| AstraZeneca | 2 | 4 |
| Novartis | 2 | 1 |
| Sanofi | 2 | 5 |
| Roche | 1 | 6 |
| Johnson & Johnson | 1 | 3 |
| Takeda | 1 | 2 |
| GlaxoSmithKline | 0 | 7 |
| Array | 3 | 153 |
| Portola Pharmaceuticals | 2 | 1,342 |
| Mylan | 2 | 52 |
| Kyowa Hakko Kirin | 2 | 46 |
| Ionis | 2 | 34 |
| Ligand | 2 | 22 |

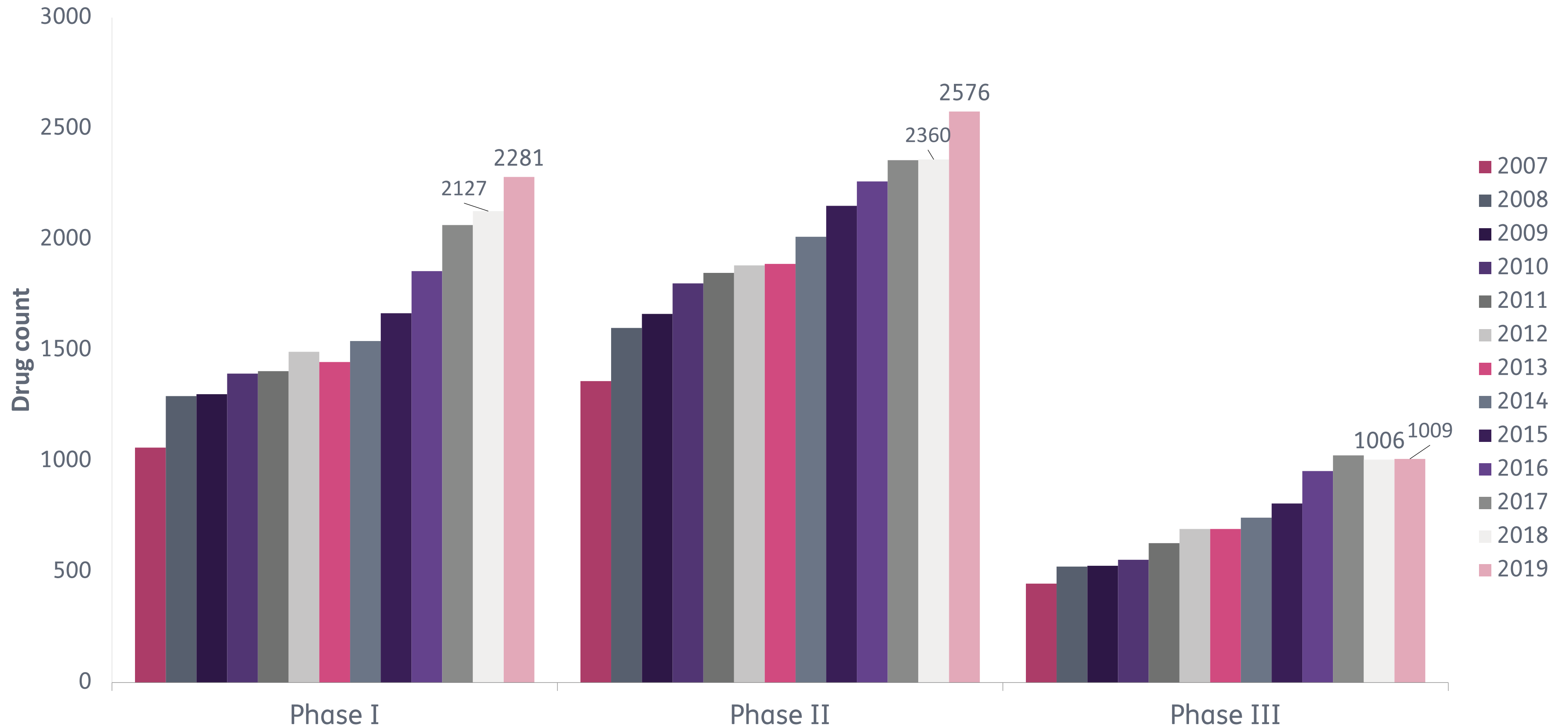
The 2019 drug pipeline in detail

Breakdown of pipeline by phase

- 6% rise at Preclinical, 4,001 drugs added to the database
- Phase I up 7.2%, Phase II by 9.2%
- But Phase III is flat, and Pre-registration/Registered down 9.2%



Trends in drug R&D by clinical phase



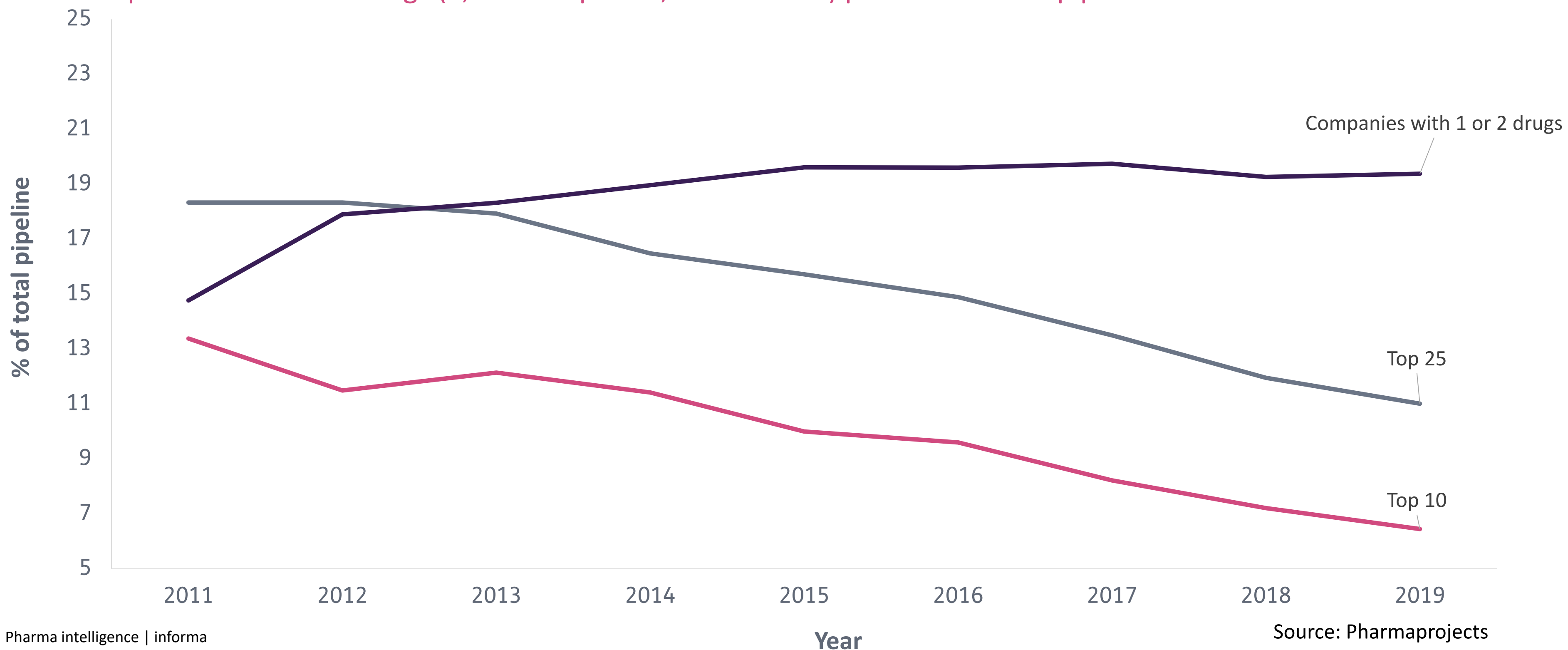
Top 10 pharma companies by pipeline size

- Novartis stays top, with Takeda up to 2nd due to Shire acquisition
- Bristol-Myers Squibb + Celgene would be joint third
- Only 2 other Top 10 companies grew pipeline size – Sanofi and Lilly

| Position 2019 (2018) | Company | No of Drugs in Pipeline 2019 (2018) | No of Originated Drugs 2019 |
|-------------------------|-------------------|--|--------------------------------|
| 1 (1) | Novartis | 219 (223) | 131 |
| 2 (9) | Takeda | 211 (164) | 99 |
| 3 (2) | Johnson & Johnson | 208 (216) | 112 |
| 4 (3) | AstraZeneca | 194 (205) | 111 |
| 5 (4) | Sanofi | 192 (179) | 93 |
| 6 (5) | Roche | 189 (191) | 106 |
| 7 (7) | GlaxoSmithKline | 177 (191) | 99 |
| 8 (6) | Merck & Co. | 176 (191) | 86 |
| 9 (4) | Pfizer | 163 (192) | 96 |
| 10 (11) | Eli Lilly | 124 (121) | 74 |

Big Pharma vs small companies – how the balance is shifting

- Top 10 companies only originating 6.5% of drugs now, was over 13% in 2011
- Top 25 providing 11.0%, down from 18.3% in 2011
- Companies with 1 or 2 drugs (2,302 companies, 53% of total) provide >19% of pipeline

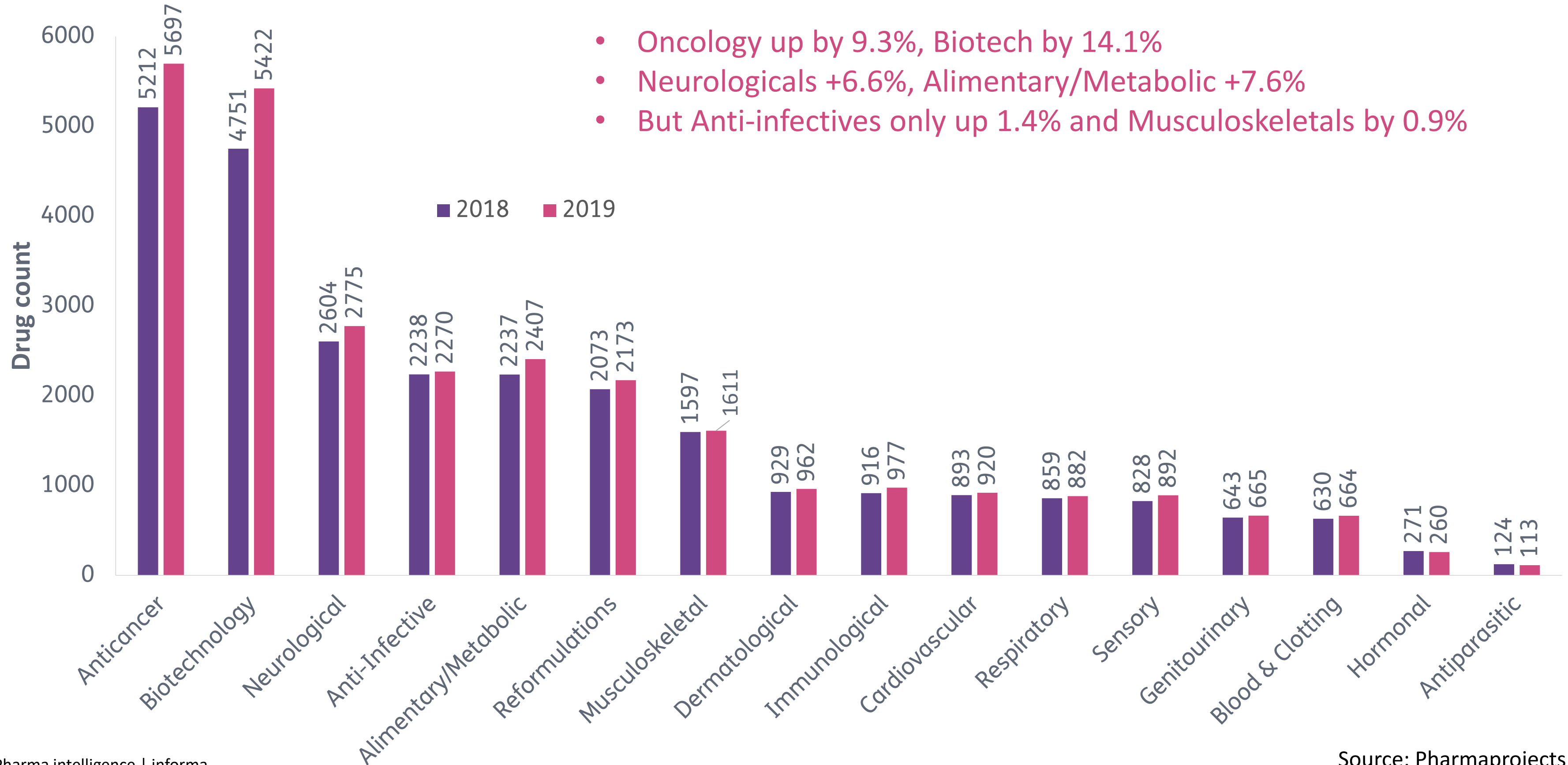


Total companies involved in pharma R&D

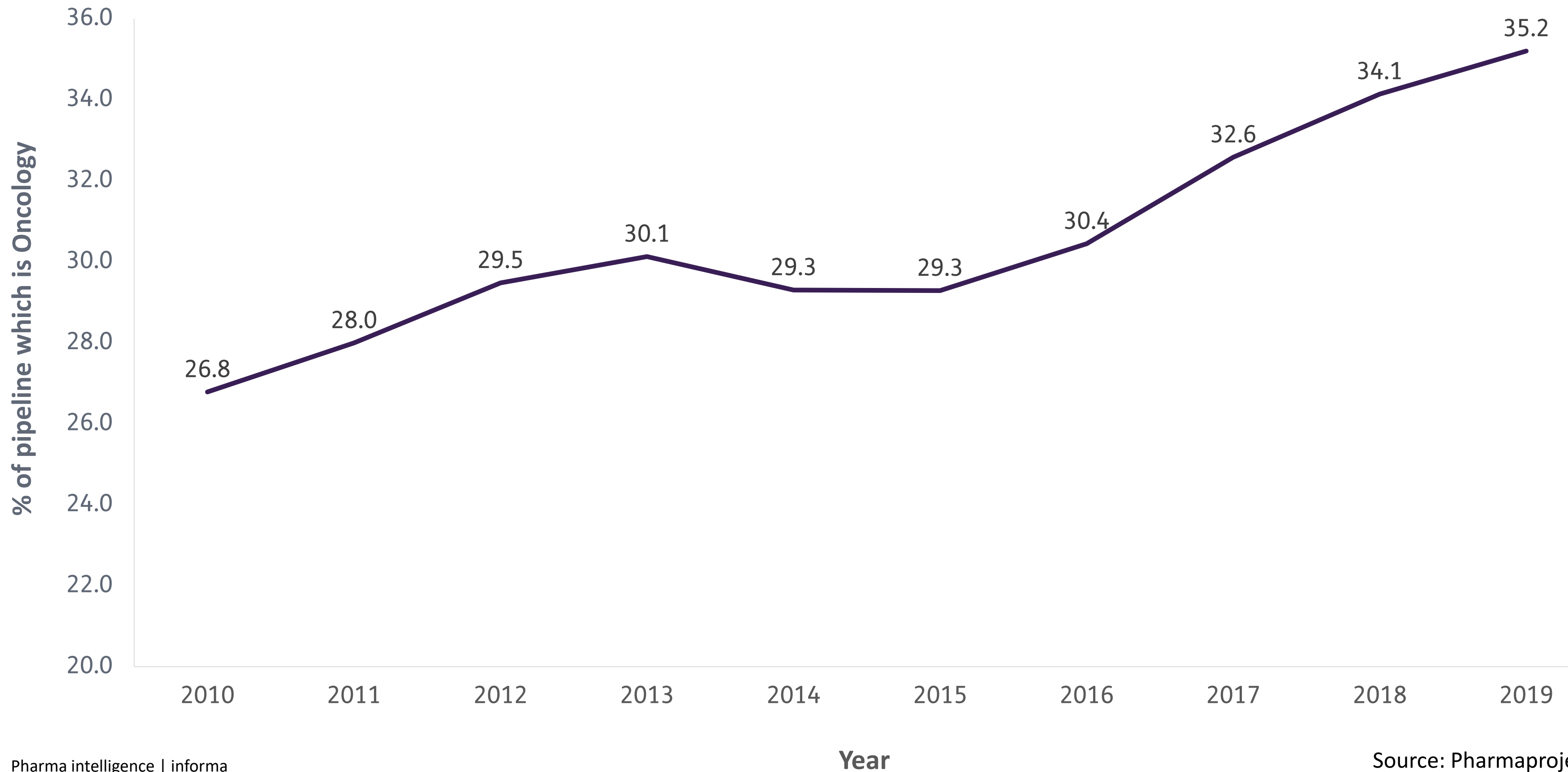
- 4.6% increase in companies, up from a 3.3% increase last year
- 772 new companies identified through 2018 (up from 670 in 2017)
- Therefore, 533 companies exited due to M&A, failure or hibernation



The R&D pipeline by Therapeutic Area



Cancer taking an ever bigger slice of the R&D pie



The rise and fall and rise of gene therapy

- Peak of 275 projects in 2003, followed by a decline
- Steep rise post-2014, success or Luxturna, CAR-T, CRISPR etc



Top 10 diseases/indications

- Breast cancer up 6.5%, NSCLC in 2nd up 7.7%. Cancers now 14 of the Top 20
- Alzheimer's and T2 Diabetes only non-cancer indications in Top 10

| Position 2019 (2018) | Disease | Number of Active Drugs 2019 (2018) | Trend |
|-------------------------|------------------------------|---------------------------------------|-------|
| 1 (1) | Cancer, breast | 774 (727) | ↑ |
| 2 (2) | Cancer, lung, non-small cell | 586 (544) | ↑ |
| 3 (3) | Cancer, colorectal | 535 (503) | ↑ |
| 4 (4) | Cancer, ovarian | 442 (434) | ↔ |
| 5 (5) | Cancer, pancreatic | 438 (430) | ↔ |
| 6 (8) | Alzheimer's disease | 405 (381) | ↑ |
| 7 (6) | Diabetes, Type 2 | 382 (407) | ↓ |
| 8 (7) | Cancer, prostate | 366 (381) | ↓ |
| 9 (9) | Cancer, brain | 360 (361) | ↔ |
| 10 (11) | Cancer, melanoma | 357 (346) | ↔ |

Top diseases/indications – 11-25

| Position 2019 (2018) | Disease | Number of Active drugs 2019 (2018) | Trend |
|-------------------------|--------------------------------------|---------------------------------------|-------|
| 11 (12) | Cancer, leukaemia, acute myelogenous | 338 (326) | ↔ |
| 12 (10) | Arthritis, rheumatoid | 335 (352) | ↓ |
| 13 (17) | Cancer, myeloma | 283 (254) | ↑ |
| 14 (15) | Cancer, head and neck | 283 (258) | ↑ |
| 15 (19) | Cancer, gastrointestinal, stomach | 276 (242) | ↑ |
| 16 (13) | Cancer, liver | 273 (272) | ↔ |
| 17 (18) | Parkinson's disease | 271 (252) | ↑ |
| 18 (14) | Pain, nociceptive, general | 266 (262) | ↔ |
| 19 (16) | Psoriasis | 260 (256) | ↔ |
| 20 (22) | Cancer, lymphoma, non-Hodgkin's | 231 (215) | ↔ |
| 21 (-) | Non-alcoholic steatohepatitis | 222 (-) | ↑ |
| 22 (21) | Cancer, renal | 221 (218) | ↔ |
| 23 (20) | Asthma | 196 (224) | ↓ |
| 24 (25) | Infection, HIV/AIDS | 189 (177) | ↔ |
| 25 (-) | Cancer, bladder | 179 (-) | ↑ |

Increasing focus on rare diseases

- 580 rare diseases being investigated now, up from 389 in 2013
- No of drugs for rare diseases up from 4,615 in 2018 to 4,953 now

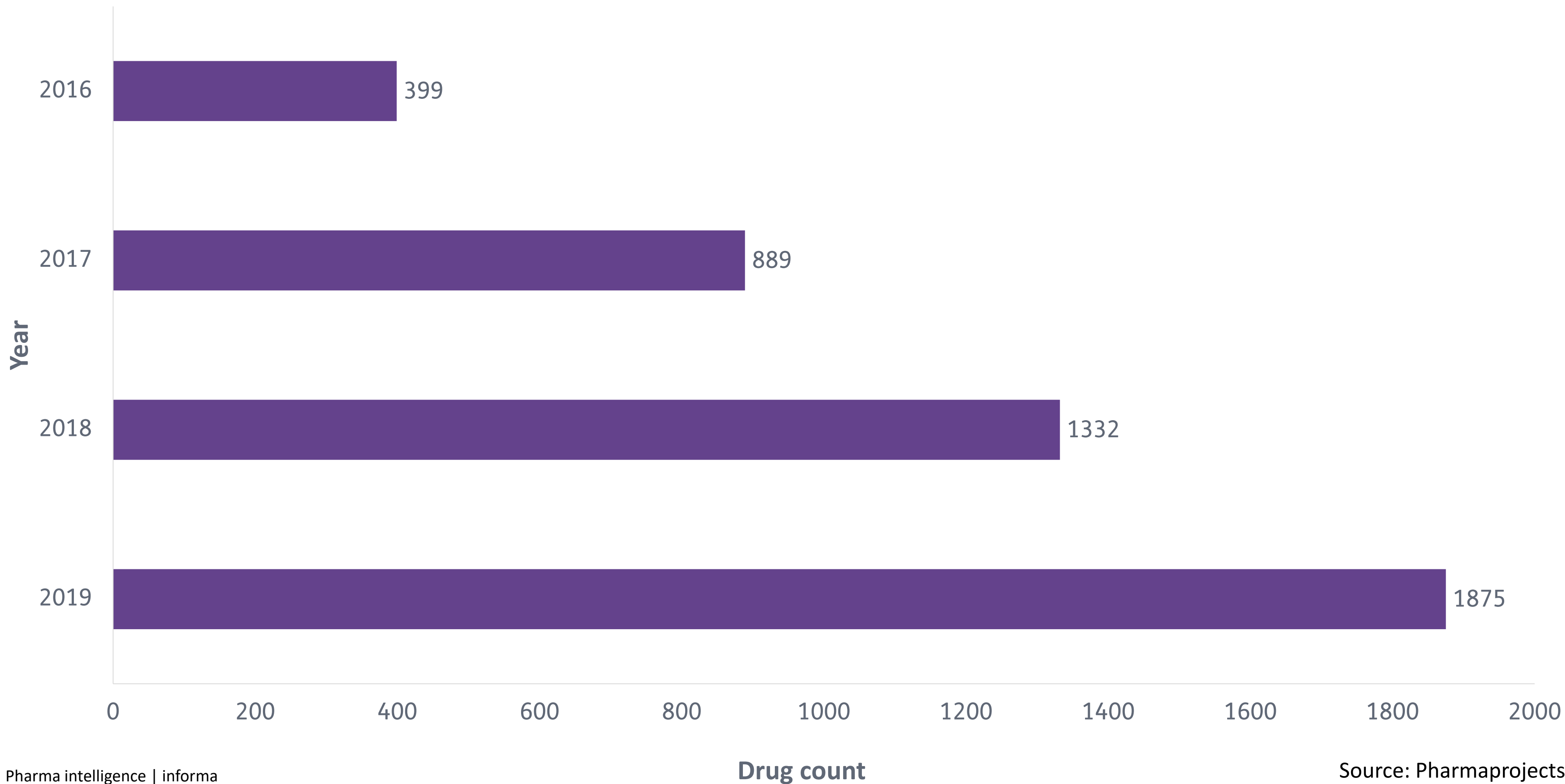


Top 10 Mechanisms of Action (Pharmacologies)

- Immuno-oncology now the most popular strategy, despite only 1.6% of drugs in late stage development
- T cell stimulant, covering CAR-T and some vaccines, up to number 3

| Position 2019 (2018) | Mechanism of Action (Pharmacology) | Number of Active Drugs 2019 (2018) | % of Compounds PR/R/L |
|-------------------------|--|---------------------------------------|--------------------------|
| 1 (2) | Immuno-oncology therapy | 1875 (1332) | 1.6 |
| 2 (1) | Immunostimulant | 1387 (1501) | 10.2 |
| 3 (11) | T cell stimulant | 404 (106) | 1.7 |
| 4 (3) | Immune checkpoint inhibitor | 327 (211) | 3.7 |
| 5 (4) | Immunosuppressant | 199 (208) | 30.7 |
| 6 (5) | Angiogenesis inhibitor | 186 (169) | 17.7 |
| 7 (6) | Vascular endothelial growth factor (VEGF) receptor antagonist | 149 (138) | 14.8 |
| 8 (7) | Apoptosis stimulant | 131 (116) | 15.3 |
| 9 (10) | Radiopharmaceutical | 122 (108) | 8.2 |
| 10 (9) | Opioid mu receptor agonist | 116 (110) | 37.9 |

The rise of immuno-oncology as a drug development strategy

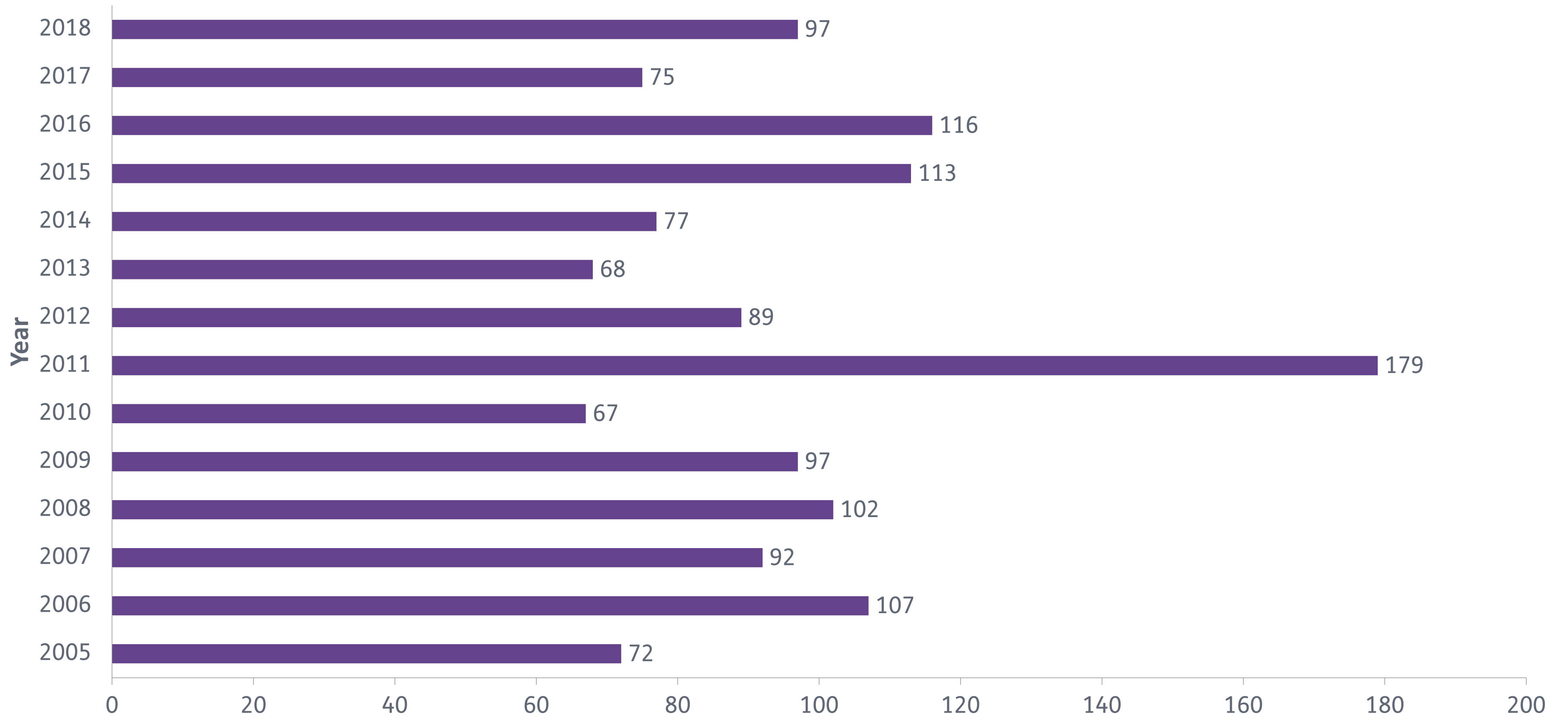


Top 10 Drug protein targets

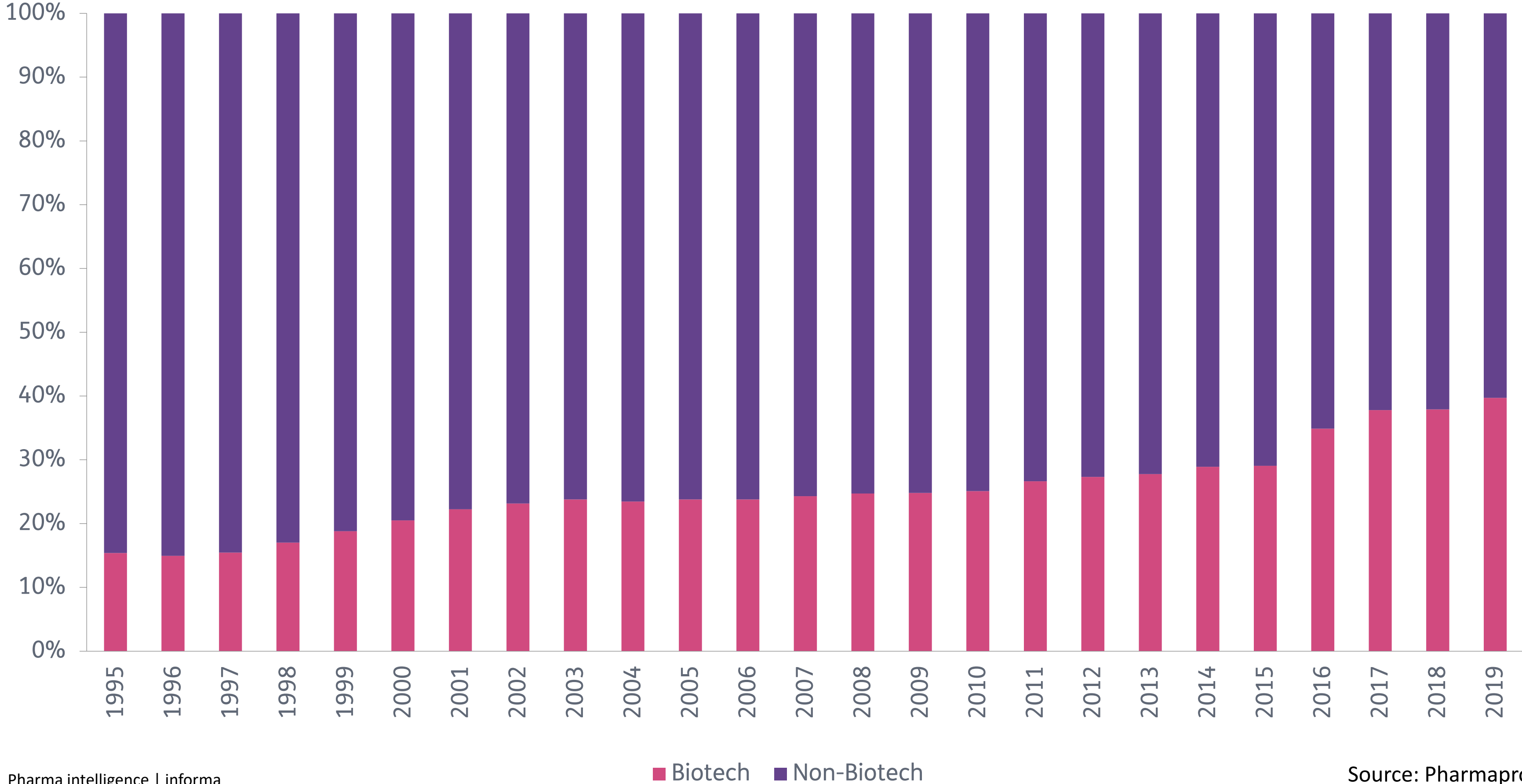
- Mu1 opioid receptor (pain/constipation) stays top
- Only 2 cancer targets in Top 10. Two diabetes targets also feature

| Position 2019 (2018) | Target | Number of Active Drugs 2019 (2018) | Trend |
|-------------------------|---|---------------------------------------|-------|
| 1 (1) | opioid receptor, mu 1 | 147 (140) | ↑ |
| 2 (2) | erb-b2 receptor tyrosine kinase 2 [<i>HER-2</i>] | 135 (120) | ↑ |
| 3 (3) | vascular endothelial growth factor A | 131 (119) | ↑ |
| 4 (5) | tumour necrosis factor | 123 (113) | ↑ |
| 5 (7) | epidermal growth factor receptor | 121 (107) | ↑ |
| 6 (4) | nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) | 113 (113) | ↔ |
| 7 (6) | prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase) [<i>COX-2</i>] | 112 (107) | ↔ |
| 8 (8) | insulin receptor | 104 (99) | ↔ |
| 9 (10) | glucagon-like peptide 1 receptor | 94 (80) | ↑ |
| 10 (9) | opioid receptor, kappa 1 | 91 (88) | ↔ |

Number of new drug protein targets identified by year



Biologicals advance towards 40% of R&D



The outlook for pharma for the year ahead

Selected key drugs approved late 2018/early 2019

- **Ultomiris** (ravulizumab) from Alexion for adults with paroxysmal nocturnal hemoglobinuria
 - Complement inhibitor, approved in US early Dec (was launched Jan 2019)
- **Elzonris** (tagraxofusp) from Stemline Therapeutics for blastic plasmacytoid dendritic cell neoplasm
 - Targeted therapy of human IL-3 recombinantly fused to truncated diphtheria toxin (was launched Jan 2019)
- **Tyvyt** (sintilimab) from Innovent and Lilly for Hodgkin's lymphoma
 - PD-1 antagonist launched in China in Feb 2019
- **Esketamine** from Johnson & Johnson for treatment-resistant depression
 - Received US approval Mar 2019 after mixed clinical results

Important approvals expected in 2019 – Part 1

- **Tenapanor hydrochloride** from Ardelyx for irritable bowel syndrome with constipation
 - First-in-class selective Sodium/hydrogen exchange (NH3E) inhibitor
- **Selinexor** from Karyopharm for multiple myeloma
 - A first-in-class inhibitor of the nuclear export protein, XPO1
- **Givosiran** from Alnylam for acute hepatic porphyria
 - A subcutaneous RNAi therapeutic which targets aminolevulinate synthase
- **Lefamulin** from Nabriva for community-acquired bacterial pneumonia
 - A potent oral and iv antibacterial with favorable pharmacokinetics

Important approvals expected in 2019 – Part 2 (biologicals)

- **Brolucizumab** from Novartis for wet age-related macular degeneration
 - Has the potential to extend the dosing intervals for intravitreal anti-VEGF therapy to once every 12wk
- **Zolgensma** (nasemnogene abeparvovec) from Novartis for spinal muscular atrophy
 - A one-time gene therapy which replaces the defective SMN1 gene
- **Zynteglo** (LentiGlobin) from Bluebird Bio for transfusion-dependent β -thalassemia
 - Uses a lentiviral vector to deliver the human beta-globin gene transfer
- **Lisocabtagene maraleucel** from Celgene for diffuse large B-cell lymphoma
 - CAR-T therapy acquired with Juno Therapeutics

Other wider issues likely to affect pharma in 2019

- **Political upheaval**
 - Brexit – uncertainty
 - Impact Of US government shutdown
 - Growth slowdown in China and ongoing China vs US trade war
- **M&A picture uncertain**
 - High valuations remain a barrier
 - Effects of US tax reform not clear cut
 - Likely one or two big mergers, others focused on acquiring specific drugs or technology
- **Pricing & market access**
 - Real-world pricing: drugs reimbursed based on their benefits, not manufacturing costs
 - High pricing 'acceptable' for curative therapies?

What does 2019 hold for biopharma? Therapeutic advances

- **New Approaches**
 - Gene therapies
 - Microbiome gaining importance
 - Genomic testing
- **Oncology**
 - New I-O combos: CAR-Ts + antibody/drug conjugates
 - Targeting disease resistant to 1L therapies
 - Tumor-agnostic: targeting common gene mutations rather than tumor types
- **CNS**
 - Much activity in Parkinson's, on disease-modifying alpha-synuclein inhibitors
 - Year of anticipation in Alzheimer's – 2020 readouts on beta-amyloid-targeting MAbs

Global R&D And Clinical Trends: What Changed In 2018, And What To Look Out For In 2019 - Summary

- The R&D pipeline continues to grow at a healthy rate
- This might be sustainable, as the past few years have delivered healthy numbers of new drugs
- Phase II failure rate remains a barrier
- Limited big M&A is underway, although top companies continue to lose share
- Cancer, and immuno-oncology in particular, ever more dominant
- In 2018 in R&D, pharma scored a try;
now it needs a conversion!

Thanks for your
attention!

Any questions?

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