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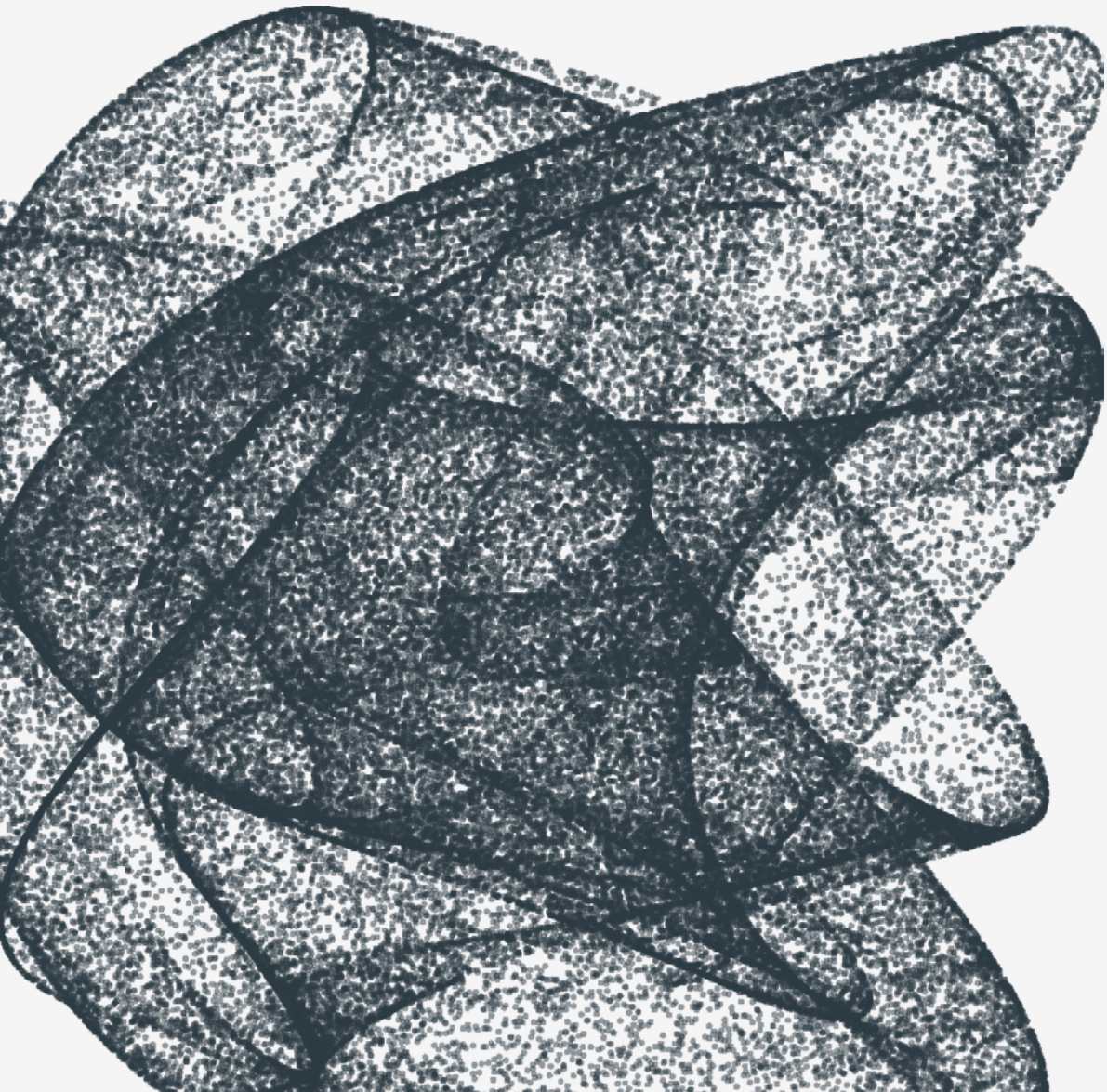
FOR HUMAN DATA SCIENCE

2019 R&D Achievements

NEW PRODUCT LAUNCHES, CLINICAL TRIAL ACTIVITY, AND INVESTMENTS



APRIL
2020

Introduction

Tracking and assessing the vitality of the life science innovation system is of importance to all healthcare stakeholders. The remarkable advances in basic science combined with improvements in translational science and approaches to clinical development have resulted in record levels of novel medicines reaching patients in recent years. Yet, there is more to be done. To increase the productivity of R&D, Human Data Science offers opportunities to drive advances across human science, data science, and technology that can enhance clinical development and influence clinical trial duration, complexity, and likelihood of success. Furthermore, Human Data Science can help address critical gaps in population health data and understanding of the natural history of disease. Proactively understanding and using this information can help stakeholders identify unmet needs in areas such as neglected and infectious disease, while also improving efforts to identify the onset of disease more accurately and quickly.

This report assesses the current status in the R&D of medicines at the end of 2019. It provides an analysis of the number of initiated clinical trials and insight into the success rate of products as they more through phases of development. The current state of innovation is explored by examining the record numbers of new active substances (NAS) launched in 2019, analyzing their features and development path, as well as the significant contributions of both NAS and non-NAS therapies.

As levels of life science venture capital activity and large pharma R&D spend continue to grow, this report also investigates the expanding pipeline of therapies still under development, examines trends among therapy areas, and analyzes the growing number of Next-Generation Biotherapeutic products, which include cell, gene, and nucleotide therapies.

The research included in this report was undertaken independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding. None of the analytics in this report are derived from proprietary sponsor trial information but are instead based on proprietary IQVIA databases and/or third-party information.

The contributions to this report from Taskin Ahmed, Marni Hall, Jeff Hodge, Michael Kleinrock, Deanna Nass, Elizabeth Powers, Bradley Smith, Terri Wallace and dozens of others at IQVIA are gratefully acknowledged.

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MURRAY AITKEN

Executive Director
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Overview

New product launches

+ On average, 40 new active substances (NAS) in the United States were launched per year over the time period of 2009 through 2019. In 2019, 50 NAS reached patients, down slightly from 59 in 2018, but higher than the historical average.

+ Hematologic malignancies and oncology drugs represent 24% of new active substances while 18% are in neurology and 16% in infectious disease.

+ Development time has not shifted significantly despite an increased number of specialty drugs and orphan indications among NAS in 2019, with the median development time from first patent filing to launch being 13.7 years for NAS products in 2019.

+ The overall percentage of NAS receiving expedited approval has increased steadily since 2015, and in 2019, 37 NAS products (74%) had at least one expedited review designation.

+ Forty percent of NAS launches in 2019 were identified by the FDA as first-in-class – drugs noted by the FDA as innovative therapies with mechanisms of action different from those of existing therapies – almost double the number in 2011.

+ Advances in patient care also occurred around new and expanded uses of currently approved products in 2019, with notable examples in infectious disease, cardiovascular/metabolic, oncology, and central nervous system disorders, expanding access to new patient populations and improving patient value through simplified dosing or formulation.

+ In 2019, 24% of NAS had single arm trials among their approval trials, up from 15% in 2018. Single arm trials are useful in smaller target populations where there are challenges conducting randomized controlled trials, and this trend is mostly driven by the growing percentage of orphan NAS launching in the United States.

+ Almost a third of drugs launched in 2019 in the United States included patient-reported outcomes (PROs) on their labels, indicating the continued significance of these instruments for clinical outcome assessments.

+ Three launched NAS in 2019 included RWE data in their pivotal trials, and one additional drug received a supplemental approval using RWE, but had launched previously in 2015

Investments

+ Life science venture capital deal activity topped $20 billion in 2019 with average deal values growing at a five-year CAGR of 12%.

+ Approximately a third of the deals were in the angel investor and seed funding category, up from 18% of deals in 2009, demonstrating a shift in the mix of venture capital life science deals from later to earlier stages of development.

+ Large pharma R&D spending grew 26% over the past five years, topping over 100 billion for the second year in a row, although expenditure was up only modestly in 2019 over 2018 levels.

Overview

Clinical trial activity

+ The number of clinical trials increased with a CAGR of 5.8% since 2014, however, the overall number of clinical trials initiated in 2019 did not increase significantly over 2018, due in part to a modest decrease in the number of initiated Phase III trials.

+ The number of clinical trials tagged as having pharmacogenomic (PGX) patient preselection/ stratification–those trials that constitute precision medicines–have increased over 50% since 2014 to a total of 972 trials.

+ The percent of trials that include a predictive biomarker increased only modestly from 14% to 17% over 10 years, indicating challenges remain both in identifying novel biomarkers and testing them in clinical development.

+ The composite success rate, which describes the likelihood of bringing a drug candidate through regulatory approval, fell from 11.1% in 2018 to 7.6% in 2019, well below the average of 12.9% for the period of 2009-2019, due to drops in success across all development stages.

+ While the composite success rate has been declining since 2015, an ever-increasing emerging product pipeline over this period suggests many products may still succeed and be brought to market in the next five years.

New product pipeline

+ The late-stage active pipeline has grown 50% since 2014, reflecting a continued push for therapies in oncology, infectious disease, and neurology.

+ The total late-stage pipeline now comprises 3,169 products with a growth of 10% from 2018 and a CAGR of 8% over the past five years.

+ There has been a 76% increase in oncology products in the late-stage pipeline over the past five years, and in 2019, oncology products account for 30% of the late-stage pipeline.

+ The gastrointestinal pipeline has seen a significant increase in NASH products, growing from 10 products in 2014 to 45 in 2019, and the number of gastrointestinal therapies in the late-stage pipeline have grown 73% in the past five years and represent 7% of the 2019 late-stage pipeline.

+ Next-Generation Biotherapeutics (NGB), defined as cell, gene, and nucleotide therapies, now make up nearly 12% of the late-stage pipeline.

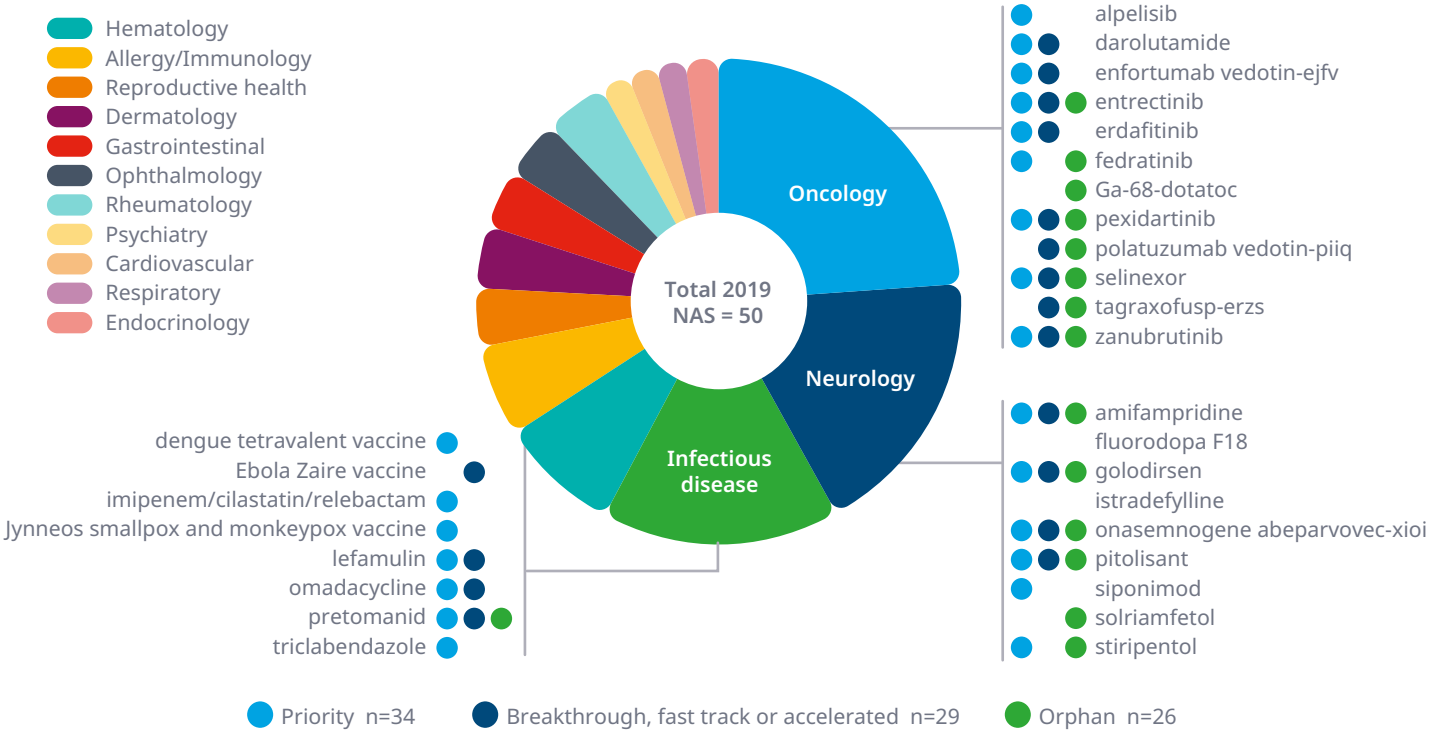
New product launches

The number of innovative and novel therapies launched in 2019 has once again surpassed the historical average. While 40 new active substances (NAS) were launched per year in the United States from 2009–2019, 50 NAS reached patients in 2019 — down slightly from the 59 NAS launched in 2018. NAS include all novel small molecule, biologic or Next-Generation Biotherapeutic (i.e., cell, gene or nucleotide therapy) products that have not been previously marketed, as well as any combination products with at least one novel molecule (see Exhibit 1).

The medicines launched in 2019 range across a wide array of therapy areas and orphan diseases. Just over half of NAS received an orphan drug designation at the time of approval, indicating they are intended to treat rare diseases that typically occur in less than 200,000 people in the United States and where there are often few treatment options for patients. In total, 24% of NAS are for hematologic malignancies and oncology indications, including lymphoma, breast and bladder cancers, while 18% are in neurology and 16% in infectious disease. The majority of launches in neurology were in orphan indications with high unmet need, such as spinal muscular atrophy (SMA) and Duchenne muscular dystrophy, while infectious disease included critical vaccines and treatments for tropical and neglected diseases.

The average time to develop these therapies from first patent filing to launch has not shifted significantly despite an increased number of specialty and orphan indications being launched in 2019 and remains a slow process. Moving from scientific breakthrough to the launch of a therapeutic medicine for the 2019 cohort of NAS took over 15 years on average, with the median

Exhibit 1: New Actives Substances (NAS) Launched for the First Time in the United States in 2019



Source: IQVIA Institute, Jan 2020
Note: Oncology includes both solid tumors and hematologic malignancies. Three drugs are notable in that they address women's health issues. Brexanolone is the first treatment approved for postpartum depression (PPD), bremelanotide is the second therapy approved for the treatment of hypoactive sexual desire (HSDD) in women, and ethinyl estradiol/segesterone acetate provides an additional option for pregnancy prevention.

development time being 13.7 years; similar to the 13.6 years of the 2018 NAS.

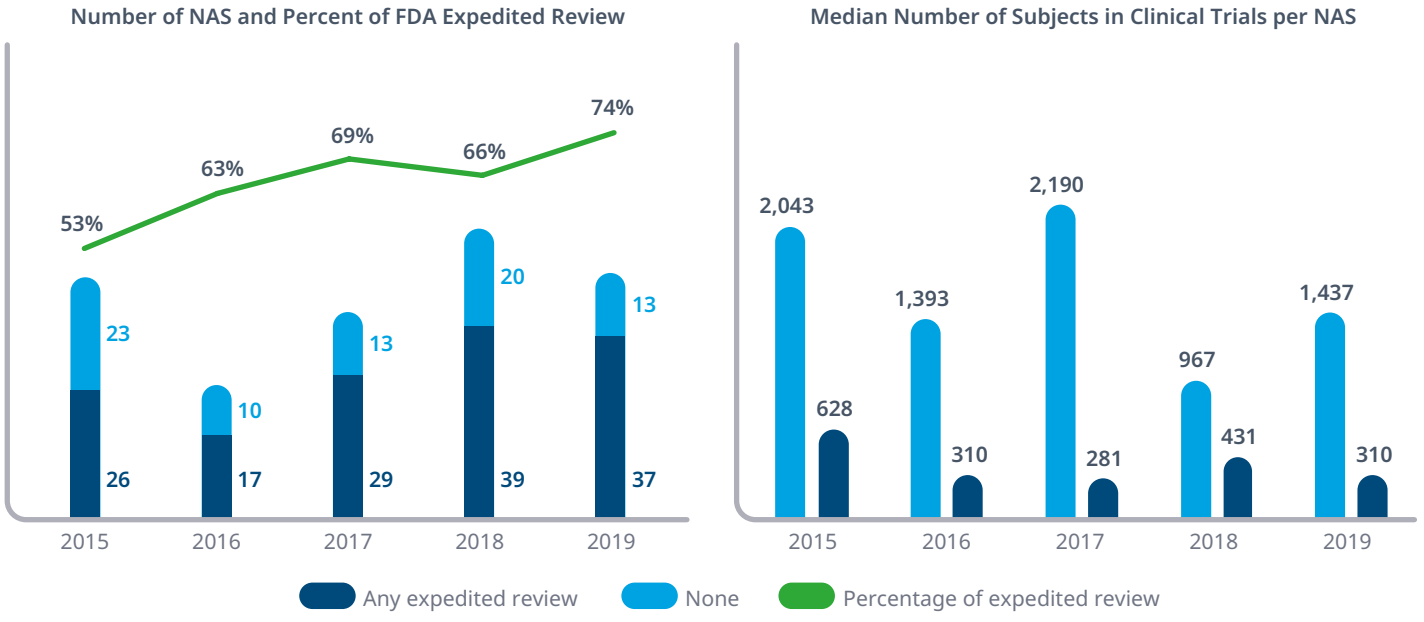
Development of medicines in areas such as rare disease continues apace. The FDA has established a number of expedited review programs for serious conditions or those with unmet need, namely, priority review, breakthrough therapy and fast track designations and the accelerated approval pathway.[1] The overall percentage of NAS receiving expedited approval has increased steadily since 2015, and in in 2019, 37 NAS products (74%) had at least one expedited review designation (see Exhibit 2).

The FDA's urgency to bring innovative therapies to patients in these areas is balanced, in part, by requiring additional confirmatory and post-marketing trials from manufacturers. For medicines with accelerated approval in 2019, the required post-approval confirmatory trials examine, on average, more than three times the number of subjects and six times the number of subject-years than pivotal trials (see Exhibit 3). This demonstrates the FDA's attempt to balance the urgency for patient access in areas of unmet need by shifting the bulk of evidence gathering supporting clinical benefit and safety into the post-approval period.

IMPROVED INNOVATION IN MEDICINES

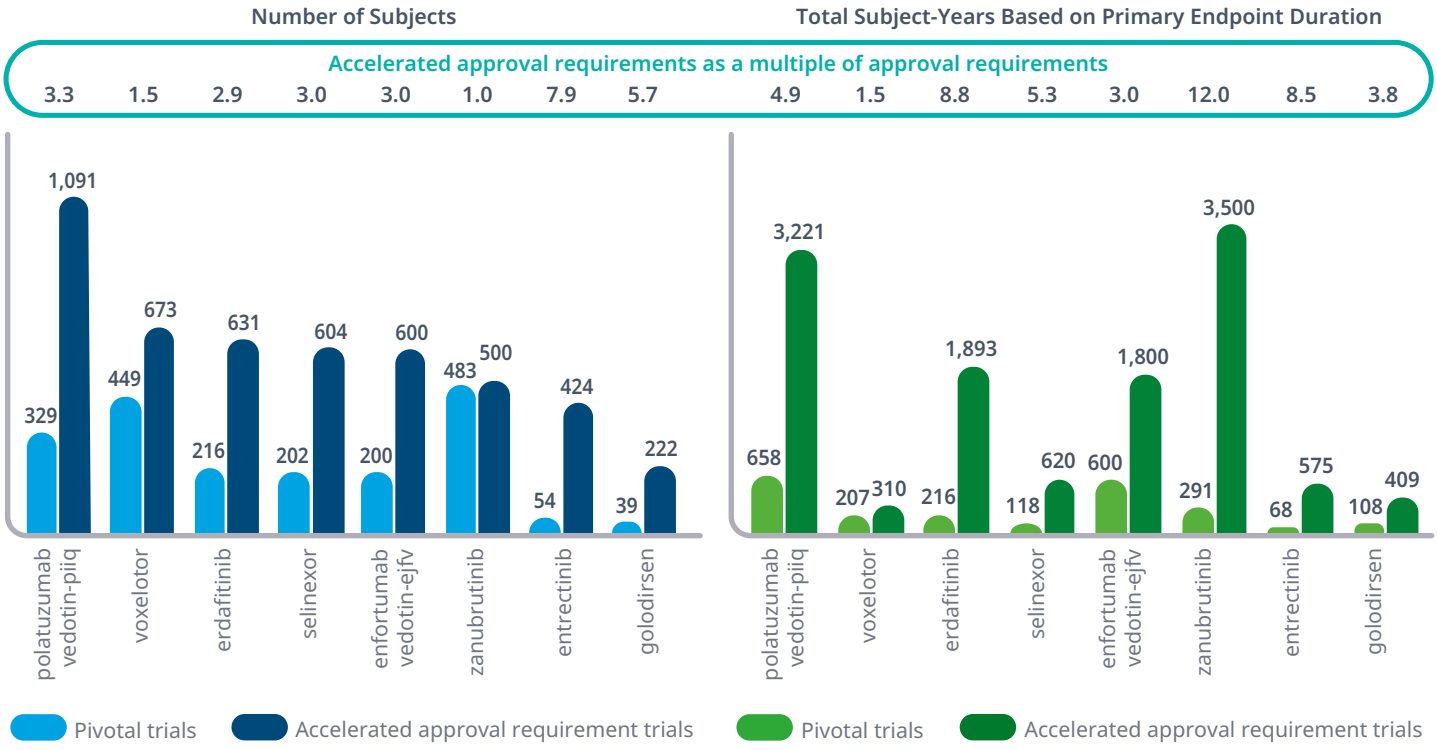
The year 2019 saw great innovation among newly launched medicines when measured by the number of novel mechanisms of actions, precision and personalized medicines, orphan designated, and specialty medicines. This furthers the trend in research and development programs to develop these types of molecules. Forty percent of NAS launches in 2019 were identified by the FDA as first-in-class – those drugs noted by the FDA as innovative therapies with mechanisms of action different from those of existing therapies – a number that has almost doubled since 2011. Specialty medicines, which are typically medicines that treat chronic, complex or rare diseases, accounted for 70% of all NAS. Seven NAS products recommended or required a specific biomarker on their label, stratifying potential patients through the use predictive biomarkers to those who would benefit most from the therapy. For example, alpelisib (Piqray)

Exhibit 2: NAS Receiving Expedited Review and Comparison to Non-Expedited NAS, 2015–2019



Source: IQVIA Institute, Jan 2020
Notes: Expedited review includes accelerated approval, priority review, breakthrough therapy and fast track designations; orphan drug designation is not included.

Exhibit 3: Attributes of Pivotal and Accelerated Approval Requirement Trials for 2019 NAS with Accelerated Approval



Source: Drugs@FDA, Clinicaltrials.gov, Feb 2020; IQVIA Institute, Feb 2020
Notes: The primary endpoint with the longest duration was selected within the clinical trial. Subject-years reflect the number of subjects in a trial times the duration of this primary endpoint.

became the first PIK3CA therapy in breast cancer, expanding treatment options in late-state, metastatic breast cancer for both men and women. Overall, the number of predictive medicines is down in 2019, from 12 products that launched in 2018 and 11 from 2017, signaling challenges in identifying and developing clinically relevant, predictive biomarkers.

2019 also brought significant breakthroughs to the treatment of rare, genetic diseases, including the approval of three novel nucleic acid therapies:

- **Onasemnogene abeparvovec-xioi (Zolgensma)**, a potentially curative gene replacement therapy for SMA that replaces the function of the nonworking or missing copy of the SMN1 gene. This is the second gene therapy approval in the United States
- **Golodirsen (Vyondys 53)**, the second antisense oligonucleotide therapy for the treatment of Duchenne muscular dystrophy
- **Givosiran (Givlaari)**, a small interfering RNA (siRNA) therapy for the treatment of acute hepatic porphyria, a family of four ultra-rare genetic diseases: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and ALA dehydratase-deficiency porphyria (ADP).

SIGNIFICANT CONTRIBUTIONS OF NON-NAS THERAPIES

Outside of NAS products there were also advances in patient care in 2019, with notable examples among combination therapies for infectious disease, cardiovascular/metabolic, oncology, and central nervous system disorders.

Infectious disease

Patient care was significantly improved in HIV and hepatis C in 2019.

- In HIV, **emtricitabine and tenofovir alafenamide (Descovy)** became the second daily oral drug combination approved for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection. Prior to this supplemental drug approval, emtricitabine and tenofovir disoproxil fumarate (Truvada) was the only FDA-approved PrEP treatment. In addition, the FDA granted approval to dolutegravir and lamivudine (Dovato) as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. This is the first two-drug, single tablet regimen for patients who have never been treated for HIV, eliminating any additional toxicity or potential drug interactions from a third drug.
- **Sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni)** received approval in pediatric patients aged 3–17 years, expanding treatment populations in hepatitis C. Treatment length for hepatitis C was also improved. **Glecaprevir and pibrentasvir (Mavyret)** received FDA approval to shorten treatment to eight weeks for patients with chronic hepatitis C and compensated cirrhosis who have never been treated, across all major genotypes of hepatitis C. Previously, standard treatment length for patients with compensated cirrhosis was 12 weeks or more.

Cardiovascular/Metabolic

The FDA granted approvals to several medications in the cardiovascular and metabolic spaces which account for two of the greatest public healthcare challenges in the United States – dyslipidemia and diabetes.

- Notably, the SGLT-2 inhibitor class is now being used to treat additional conditions associated with diabetes, with **dapagliflozin (Farxiga) and canagliflozin (Invokana)** receiving approvals to treat cardiovascular disease in diabetic patients and diabetic kidney disease, respectively. Dapagliflozin was approved to reduce the risk of hospitalization for heart failure in Type 2 diabetes patients, and the manufacturer has received fast track designation and priority review from the FDA for dapagliflozin's use in heart failure with reduced ejection fraction (HF-rEF) patients with or without Type 2 diabetes. Canagliflozin received an additional approval to treat diabetic kidney disease and reduce the risk of progression to end-stage kidney disease – the first Type II diabetes medication with a kidney disease indication. These events demonstrate an overlap in treatment options across comorbidities faced by diabetic patients, though this class is likely to rapidly expand to treat cardiovascular disease and kidney disease in non-diabetic patients as well. Along a similar line, **icosapent ethyl (Vascepa)**, used to treat adults with severe elevations (≥500 mg/dL) in triglyceride levels, was the first drug the FDA approved as an adjunct therapy to reduce the risk of cardiovascular events in this high-risk patient population.

In the future, the utility of the SGLT-2 inhibitor class may extend beyond solely diabetes to include additional diseases, blurring the line between kidney, metabolic, and cardiovascular disease treatments.

Treatment of diabetes was further advanced in 2019 by therapies offering improvements in patient experience and adherence.

- The first non-injectable glucagon product, **Baqsimi** nasal powder, and a pre-mixed, glucagon autoinjector, **Gvoke Hypopen**, were approved as emergency rescue treatments for severe hypoglycemia. These products offer a significant advancement for diabetes patients experiencing a severe hypoglycemic event. Prior to these approvals, glucagon treatment and administration required a multi-step mixing process and an injection that posed challenges for caregivers in an emergency and often required training. The new ready-to-use rescue treatments give diabetes patients more autonomy and the ability to treat their own disease in times of distress.
- The first oral GLP-1 agonist **semaglutide (Rybelsus)** was approved by the FDA. Prior to this approval, all GLP-1s had been injectables. The new oral option contains the same molecule as injectable semaglutide (Ozempic), yet offers more flexibility for patients wanting to avoid injections. This advance may help increase adherence to these medications which decrease diabetes symptoms and delay disease progression.

In cardiology, there were several approvals for pediatric populations, increasing the utility of these medicines in vulnerable patients with high unmet need.

- **Dalteparin sodium (Fragmin), sacubitril/valsartan (Entresto), and ivabradine (Corlanor)** were approved by the FDA for pediatric populations. Dalteparin sodium was approved for use in infants as young as one month old to reduce the recurrence of symptomatic venous thromboembolism. The latter two drugs were approved for use in pediatric patients to treat heart failure as young as one year old or six months old, respectively.

Advances in patient care also occurred around new and expanded uses of currently approved products in 2019, expanding access to new patient populations and improving patient value.

Oncology

In 2019 there were advances in oncology treatment options across a wide range of indications and patient populations.

- Among notable supplemental approvals, **acalabrutinib (Calquence)** was approved for the treatment of adults with chronic lymphocytic leukemia or small lymphocytic lymphoma, and **lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda)** was approved for advanced endometrial carcinoma. Importantly, acalabrutinib and lenvatinib received supplemental approvals through Project ORBIS, an initiative from the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology drugs among the FDA, the Australian Therapeutic Goods Administration, and Health Canada.[2] Pembrolizumab continued to gain regulatory approvals in 2019, adding an additional six indications, including first-line treatment of head and neck squamous cell carcinoma, and esophageal cancer, bringing the total number of its approved indications to over 20.[3] Also of note was the expanded approval of the PARP inhibitor niraparib (Zejula) for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer in previously treated patients whose cancer is homologous recombination deficiency (HRD) positive. In 2017, niraparib became the first PARP inhibitor to be approved by the FDA that did not require BRCA mutation or other biomarker testing, but the expanded indication in 2019 is now

The percentage of NAS approved with single arm trials has increased from 15% in 2018 to 24% in 2019. Single arm trials are useful in smaller target populations where there are challenges conducting randomized controlled trials.

associated with a companion diagnostic to determine HRD status, allowing for patients beyond those with a BRCA-positive (BRCA+) mutation to be eligible for this type of targeted therapy.

- Therapies also gained approvals for use earlier in the course of disease and as earlier lines of therapy, expanding treatment options for patients. **Daratumumab (Darzalex)**, which had been approved only for patients with multiple myeloma who were unsuccessfully treated with other therapies, is now approved in newly diagnosed patients who are ineligible for a bone marrow transplant. **Ado-trastuzumab emtansine (Kadcyla)** was additionally approved for patients with early HER-2 positive breast cancer; previously it was approved in HER-2 positive metastatic breast cancer, a significant advance in the treatment of breast cancer.

Central Nervous System Disorders

Neurology and psychiatry both saw significant advances in 2019. For example,

- In neurology, **eculizumab (Soliris)** became the first FDA treatment for adults with neuromyelitis optica spectrum disorder (NMOSD), a rare disorder that can cause blindness and paralysis, leading to disability or death.
- **Cladribine, under the brand name Mavenclad**, was approved in the United States for the treatment of relapsing-remitting multiple sclerosis (RRMS) and secondary-progressive multiple sclerosis (SPMS), making it only the second disease-modifying therapy to ever be approved for SPMS. Previously, cladribine had approvals in oncology and in 2017 was approved for the treatment of RRMS outside the United States.
- **Galcanezumab-gnlm (Emgality)** was among the first calcitonin gene-related peptide (CGRP) antagonists approved for the prevention of migraine headache in 2018, and in 2019, became the first approved treatment for episodic cluster headache, a painful form of headache that occurs in clusters over a period of weeks or months.
- Psychiatry saw a major advancement in patient care in 2019, with the approval of **esketamine nasal spray (Spravato)** for treatment-resistant depression. Although ketamine has been approved and available since the 1970's as an injectable anesthetic, the approval of esketamine nasal spray for treatment-resistant depression addresses a substantial unmet need for a molecule that brings a new mechanism of action to treatment-resistant depression, as well as being efficacious and fast-acting in this patient population.

ATTRIBUTES OF CLINICAL DEVELOPMENT

Randomized controlled and single arm trials

Randomized controlled trials (RCT) continue to be the gold-standard when submitting to regulatory agencies, with the percentage of NAS including RCTs in their regulatory submission packages averaging 79% since 2015 and representing 74% of 2019 NAS. Overall, the percentage of NAS approved with single arm trials has increased from 15% in 2018 to 24% in 2019. Single arm trials are useful in smaller target populations where there are challenges conducting RCTs,[4] and this trend is mostly driven by the growing percentage of orphan NAS launching in the United States.

Patient-reported outcomes

Nearly a third of drugs launched in 2019 in the United States included patient-reported outcomes (PROs) on their labels, indicating the continued significance of these instruments for clinical outcome assessments. In some diseases, there may be no established quantifiable way to measure efficacy, necessitating instruments to record and measure qualitative feedback from a patient. PRO instruments allow the patient to describe their own health and can be measured by self-report, interview, or through specific PRO assessments measures, such as pain or sleep quality scales. There is great potential for PRO information to be captured via digital tools, such as through the use of e-diaries, but it is unclear at this time if digital tools were used to report PRO evidence for the 2019 NAS. Over half of the PROs included on product labels in 2019 were primary endpoints from clinical trials; however, despite their ubiquity, there was little novelty in the PRO measurements themselves, with none of the questionnaires copywritten later than 2007. For example, clinical trials for the NAS pitolisant (Wakix) and solriamfetol (Sunosi) assessed sleepiness using the Epworth Sleepiness Scale (ESS), an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities which was introduced in the 1990's. At a macro level, the type of information captured by PROs can be useful as health assessments to measure patient outcomes from healthcare interventions, or to compare patient outcomes across providers.[5] Collecting and analyzing patient defined outcomes from clinical trials and in the post-marketing period is likely to improve the value patients derive from care.[6]

Real World Evidence

Drug launches in 2019 continued to incorporate real world evidence (RWE) in regulatory approval packages. Three launched NAS in 2019 included RWE data in their pivotal trials: prucalopride (Motegrity), onasemnogene abeparvovec-xioi, and entrectinib (Rozlytrek).[7,8,9] An additional drug, palbociclib, originally launched in 2015, received a supplemental approval using RWE in 2019. Of note, prucalopride (Motegrity), which was approved for chronic idiopathic constipation in 2018,[7] relied, in part, on a pharmacoepidemiology study using European health records and claims of patients already taking the drug in Europe for its initial approval. The study demonstrated cardiovascular safety, and the FDA accepted the study in place of a year-long controlled cardiovascular safety trial. However, the FDA did note limitations of the study, which included potential bias due to confounding risk and differences in observation time between the prucalopride and control cohort, despite propensity score matching. This underscores the importance of clear and stringent trial design for RWE for regulatory submissions.

Despite recent advances and interest in RWE's many applications, regulators remain cautious of its use in new drug submission packages. The use of RWE in pre-approval trials are distinct from the use of RWE in post-marketing trials, as the FDA has historically used real world data (RWD) and RWE to monitor post-market safety and adverse events.[10,11] To date, the FDA has approved only 18 drugs that have leveraged RWE for initial approval, which included use as external or historical controls in the single-arm trial context or data from case reports and expanded access protocols, and approved an additional two for supplemental indications.[7,12,13,14] However, the FDA is poised to expand the use of RWE, through the approval of the 21st Century Cures Act,[10] as well as the most recent PDUFA VI reauthorization, which currently directs the FDA to further explore RWE in a regulatory context.[15]

Three launched NAS in 2019 included RWE data in their pivotal trials: prucalopride (Motegrity), onasemnogene abeparvovec-xioi, and entrectinib (Rozlytrek).

Investments

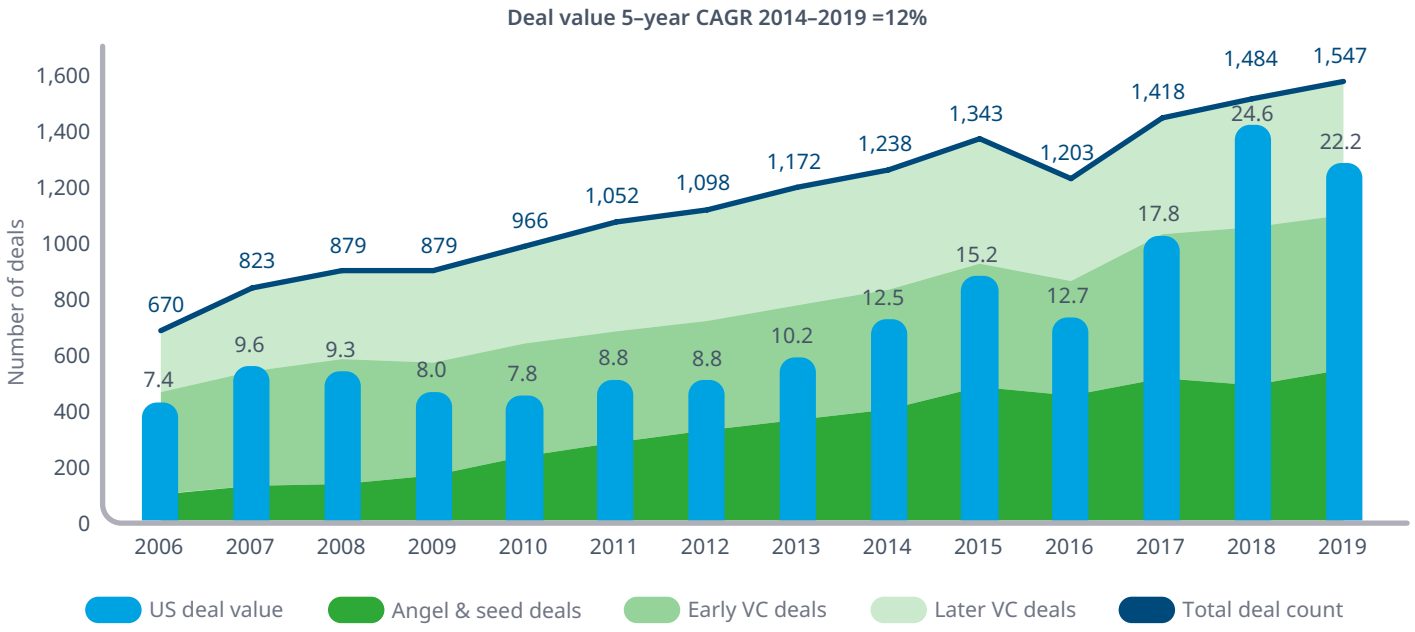
DEAL ACTIVITY

Over 1,500 life science venture capital deals closed in 2019 with an overall value of over $22 billion (see Exhibit 4). Venture capital deals have been rising steadily since 2006, excepting a dip in 2016. Approximately a third of the deals were in the angel investor and seed funding category, up from 18% of deals in 2009, demonstrating a shift in venture capital life science deals from later to earlier stages of development.

The value of life science venture capital deals continues to grow, with a five-year CAGR of 12% from 2014–2019, despite a slight decline from a record-breaking $24.6 billion in 2018. Growth in 2019 was offset in part by the U.S. government policies such as tariffs[16] and stricter standards from the Committee on Foreign Investment in the United States (CFIUS).[17] This is causing a shift in strategies for life science companies, forcing them to balance greater regulatory burden on foreign investments against a desire to access foreign markets.[17] While there was a reduction in deal activity in the life sciences sector in 2019, average mergers and acquisitions (M&A) and partnering announced deal values rose, especially reflecting Bristol-Myers Squibb's acquisition of Celgene for $73 billion and AbbVie's acquisition of Allergan for $63 billion.[18]

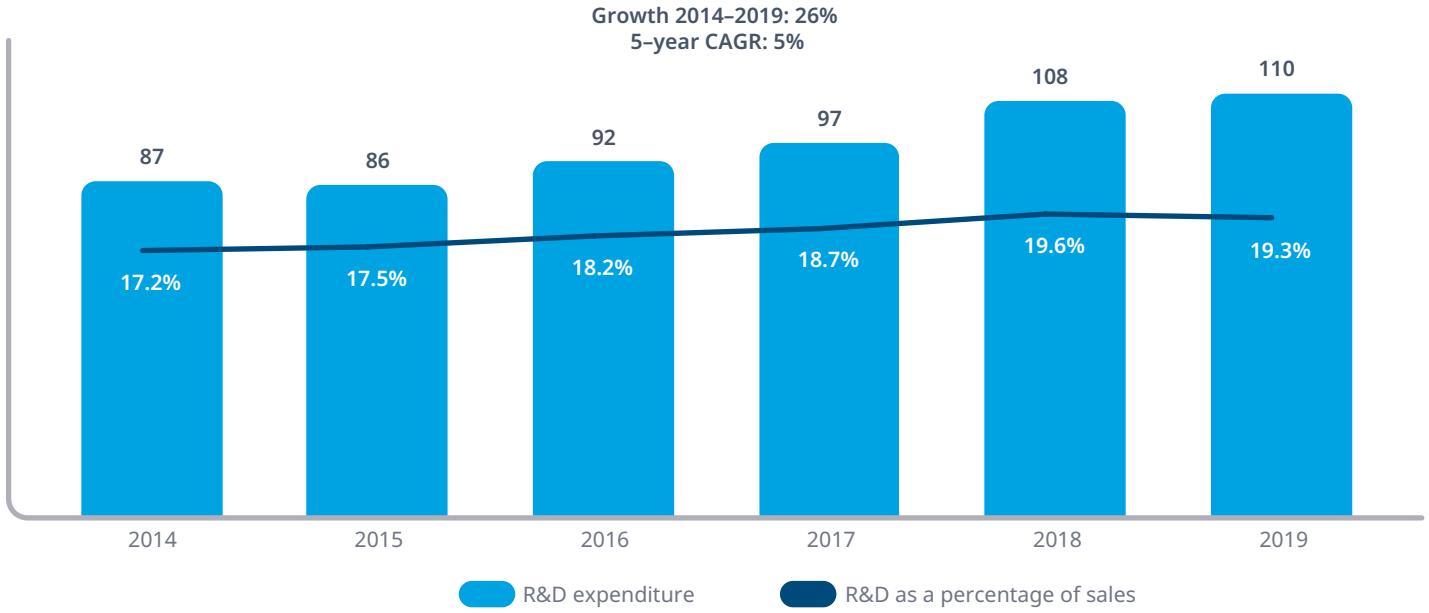
More than 1,500 life science venture capital deals closed in 2019 with an overall value of over $22 billion.

Exhibit 4: U.S. Life Science Venture Capital Deal Value in US$Bn and Number of Deals Closed by Type, 2006–2019



Source: Q4 2019 PitchBook-NVCA Venture Monitor. Accessed Jan 2020. Available from: https://pitchbook.com/news/reports/q4-2019-pitchbook-nvca-venture- monitor
Notes VC = Venture Capital.

Exhibit 5: Large Pharma R&D Spending in Total and as a Percentage of Sales 2014–2019, US$Bn



Source: Data taken from company financial statements; IQVIA Institute, Feb 2020
Notes: CAGR = Compound annual growth rate. Companies include: AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer Roche, Sanofi, and Takeda. There are often year-to-year variations in companies' reporting of R&D spend due to financial charges for failed programs that are included in the year the charges are recognized in earnings reports.

LARGE PHARMA R&D SPENDING

For the second year in a row, the 15 largest pharmaceutical companies together recorded more than $100 billion in total research and development expenditure across their businesses, up 26% since 2014 (see Exhibit 5). Overall, total research and development (R&D) spending reported by these companies has increased substantially from 2014–2019, with a five-year CAGR of 5%, and is now at $110 billion. The mix of top 15 pharma companies has shifted and included the following companies in 2019: AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. R&D spending as a percentage of sales among large pharma companies has increased over the same period. In 2019, R&D represented 19% of total sales, up from 17% in 2013. These investments in medical innovation are being made across a more diverse range of disease areas, mechanisms, and companies.

The 15 largest pharmaceutical companies together recorded more than $100 billion in total research and development expenditure across their businesses, up 26% since 2014.

Clinical Trial Activity

CLINICAL TRIAL ACTIVITY

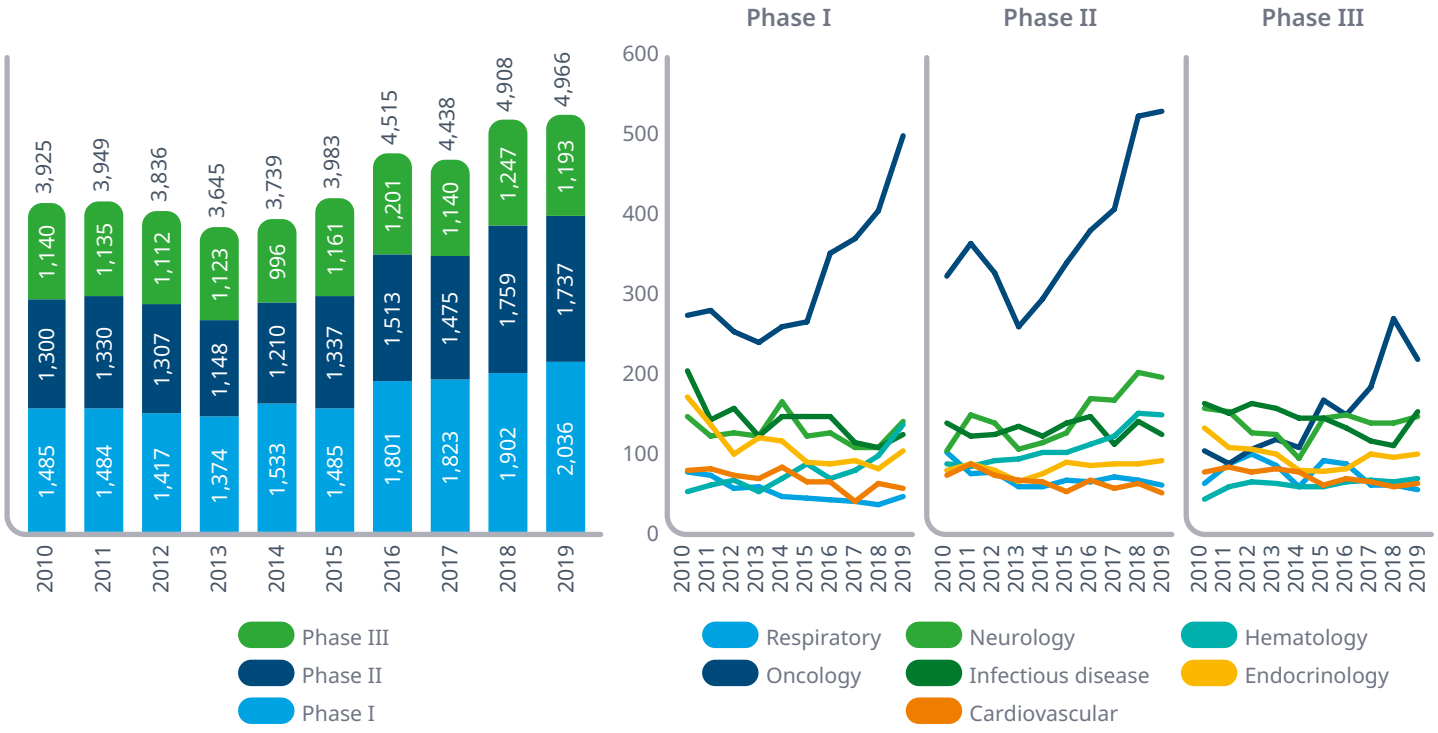
Clinical development activity has grown steadily since 2010, corresponding to a larger-than-average number of launches in 2018 and 2019 (see Exhibit 6). Overall, the number of clinical trials has increased with a CAGR of 5.8% since 2014, but the overall number of clinical trials initiated in 2019 did not increase significantly over 2018, due in part to a modest decrease in the number of initiated Phase II and III trials.

The total number of Phase I and Phase II trials has increased by 38% since 2014. Specifically, Phase I trials have increased at a CAGR of 5.8% since 2014, and Phase II trials have increased at a CAGR of 7.5%. Growth in Phase I and Phase II trials is primarily due to an increase in the number of oncology trials, which represented approximately a third of all initiated trials in Phase I and II in 2019.

Respiratory, neurology, endocrinology, infectious disease and cardiology also contributed significantly to the total number of trials and represent 34% of Phase I and 29% of Phase II trials, combined. In Phase II, there has been notable growth in the number of initiated neurology trials and in hematology from 2010 to 2019. These areas have seen an increase in the number of trials by approximately 87% and 68%, respectively, over that period.

The total number of initiated Phase III trials has declined by 4% since 2018 to just under 1,200 trials in 2019. Overall, Phase III oncology trials have increased significantly since 2014 at a CAGR of 14.7%; however, this trend includes a 18% drop between 2018–2019. The growth of Phase III oncology trials is tempered by the shift in registrational trials to earlier phases in this area. The number of infectious disease trials did increase by 36% over 2018, but this was not enough to offset declines in oncology and other therapy areas.

Exhibit 6: Total Number of Clinical Trials by Phase and by Select Therapy Areas, 2010–2019



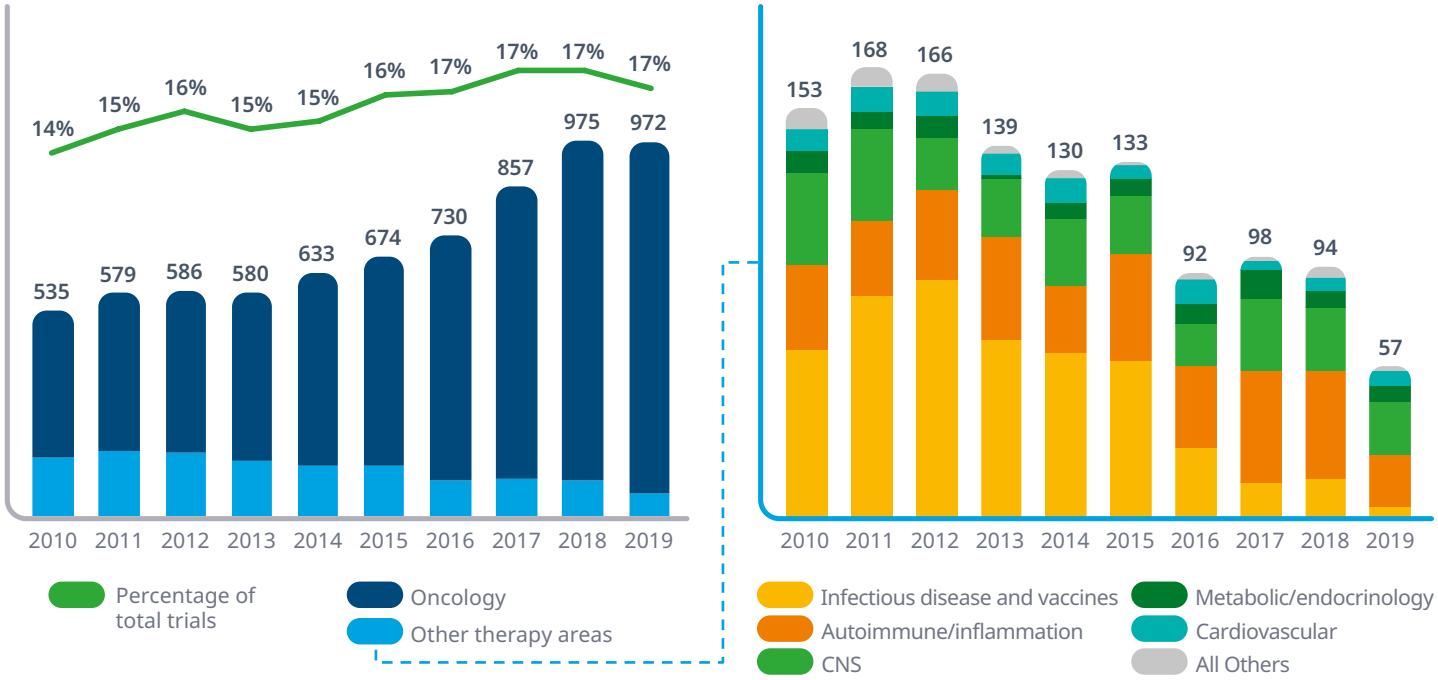
Source: Clarivate Analytics Cortellis, Mar 2020; IQVIA Institute, Mar 2020

Notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Trials were industry sponsored and device trials were excluded.

The absolute number of clinical trials tagged as having pharmacogenomic (PGX) patient preselection/stratification biomarkers increased by more than 50% since 2014 to a total of 972 trials (see Exhibit 7). These trials incorporate pharmacogenomic and/or pharmacogenetic analysis to allow predictions of patient response, tolerability or dosage. The overall share of these predictive biomarker trials out of all clinical trials remains flat, increasing modestly from 14% to 17% over 10 years, showcasing that there are still challenges both in identifying novel biomarkers and testing them in clinical development. In particular, identification of novel biomarkers for use in clinical development programs face significant hurdles, such as having a robust understanding of a particular disease's etiology and pathogenesis and adequate biomarker qualification and validation, among others.[19,20] In the future, the use of real world evidence (RWE) from clinical trials and other sources, such as data from patient engagement with digital health tools and wearables, can support the discovery and evidence gathering for novel predictive biomarkers and allow their successful incorporation into future trials.[21,22]

Oncology trials account for the greatest number of predictive biomarker trials, which nearly doubled since 2010, from 382 to 915 trials, and account for 94% of all PGX trials in 2019. However, the percent of oncology trials that were tagged with a predictive biomarker has not changed substantially since 2010, increasing from 40% of all oncology trials in 2010 to 45% in 2014 and declining to 42% in 2019. The number of precision biomarker trials outside of oncology have declined by over 60% since 2010. In particular, infectious disease trials have declined by over 90% since 2014, due in large part to a drop in the number of predictive biomarker trials for hepatitis C (98% decrease since 2012, in part due to the successful development of hepatitis C therapies that are no longer

Exhibit 7: Number of Clinical Trials with Pharmacogenomic Biomarkers in Total and by Select Therapy Areas, 2010–2019



Source: Trialtrove, Pharma Intelligence, Feb 2020; IQVIA Institute, Feb 2020
Notes: PGX = Pharmacogenomic. CNS = Central Nervous System Disorders. Biomarker trials were identified using the following trial tags: PGX-biomarker identification/evaluation, PGX-pathogen and PGX-patient preselection/stratification. PGX trials are those that incorporate pharmacogenomic and/or pharmacogenetic analysis. Trials were industry only and interventional. Terminated trials were excluded. Phase I through Phase III included. The number of PGX tagged oncology trials tagged from 2010-2019 was 5,889. For non-oncology trials, from 2010 to 2019, the total number of PGX tagged trials were: infectious disease and vaccines, n=484; metabolic/endocrinology, n=67; autoimmune/inflammation, n=327; cardiovascular, n=70 ; CNS, n=242; all others, n=40

genotype-specific) and HIV (95% decrease since 2010 in part due fewer products in development that require pharmacogenomic testing for tolerability), while CNS and autoimmune PGX biomarker trials both declined by approximately 20% in this period.

SUCCESS RATES

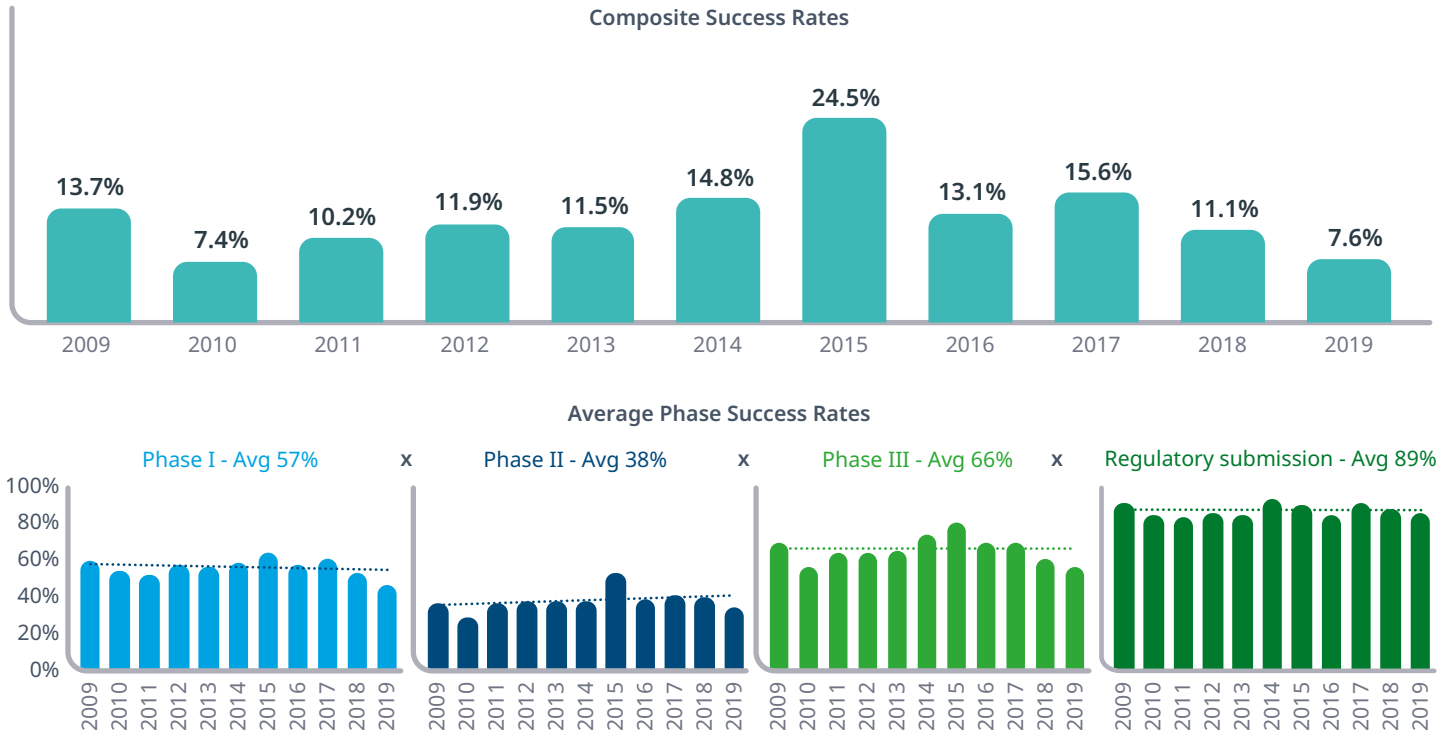
As clinical trial activity has increased, the composite success rate for drugs — which represents success of products at the start of human trials in Phase I through the regulatory decision to enable marketing — has declined in recent years (see Exhibit 8). Although composite success rates have fluctuated over the past decade, the most recent shift from 11.1% in 2018 to 7.6% in 2019 both fall well below the average of 12.9% for the period of 2009–2019 and were driven by success rates falling across all development stages. The success rates in Phase I and Phase II fell by about 12% and 13%, respectively, since 2018, while Phase III dropped by 8% and pre-registration by only 2% in the same time frame.

The composite success rate fell from 11.1% in 2018 to 7.6% in 2019, well below the average of 12.9% for the period of 2009-2019, due to drops in success across all development stages.

Although the composite success rate has been declining since 2015, an ever-increasing emerging product pipeline over this period suggests many products may still succeed and be brought to market in the next five years.

The mix of drug types under development and the number of drugs per therapy area changed during the past decade with a shift toward more oncology, biologic and specialty drugs. Among these, the cumulative

Exhibit 8: R&D Composite Success Rate and Average Phase Success Rates Phase I to Filing, 2009–2019



Source: IQVIA Pipeline Intelligence, Feb 2020; IQVIA Institute, Feb 2020

success rate for oncology has dropped from a high of 28.7% in 2015 to 7.1% in 2019. The relatively low success rate for oncology is in part due to trial complexity as well as from Phase II trials imperfectly promoting candidates to Phase III.[23]

Therapy areas with a 2019 success rate include gastrointestinal/NASH at 17.1% and immune system disorders at 16.5%, followed by neurology at 9.8%. A number of notable neurology products were approved in 2019, including for SMA, Duchenne muscular dystrophy, multiple migraine and Parkinson's disease products, but success in this therapy area was tempered by multiple failures for Alzheimer's disease, among others. Vaccines for infectious diseases had the lowest composite success rate at 4.1%, in part due to specific challenges including patient recruitment and retention, and limited understanding of how to trigger immune response to deliver disease-specific protection.

Success rates for rare disease products in 2019 were above the 10-year average for all drugs, at 15%. Similar to oncology, rare disease product success rates peaked in 2015 but have seen a decline through 2019. Challenges in clinical development for rare diseases include: complex biological processes, lack of understanding of underlying etiologies, multiple disease variations or subtypes leading to different disease progressions or clinical presentations, and difficulties in recruiting for clinical trials due to inherently small patient populations.[24,25] Despite these challenges, clinical development for rare diseases remains a priority for drug manufactures, policymakers, and patients, with 52% of NAS launches in the United States receiving an orphan drug designation in 2019.

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New Product Pipeline

OVERVIEW

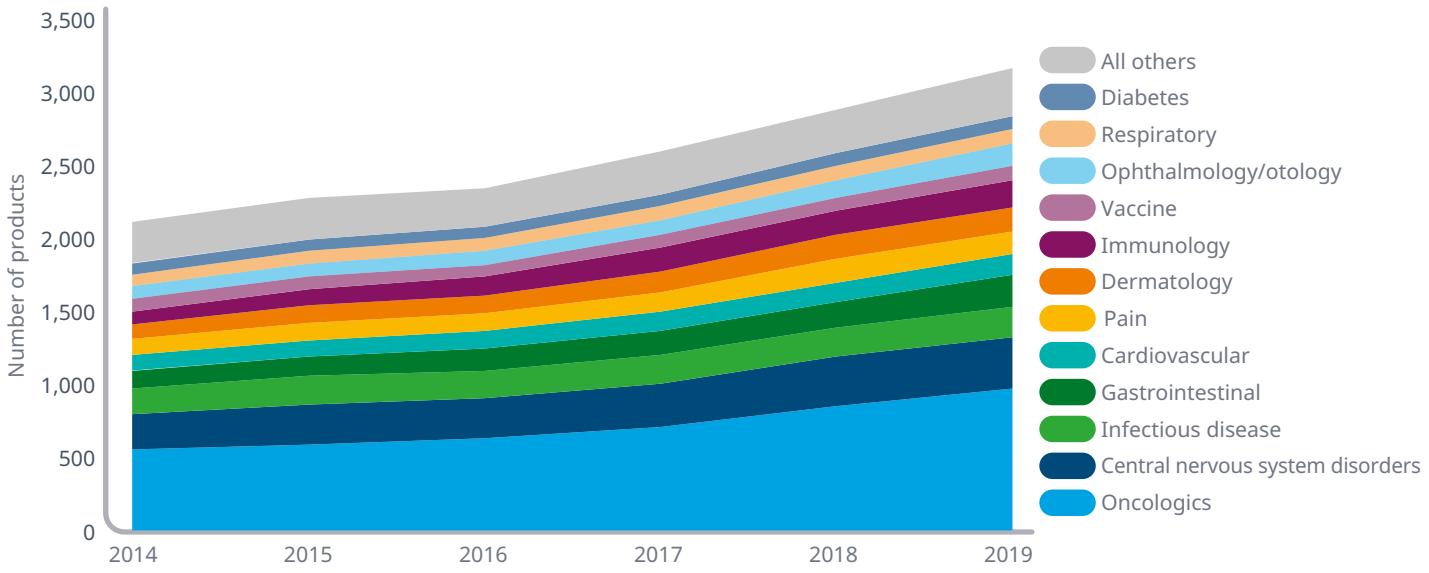
The late-stage active pipeline bodes well for future innovation in medicines, having grown 50% since 2014, reflecting a continued focus within neurology, infectious disease, and oncology (see Exhibit 9). Overall, the total late-stage pipeline comprises 3,169 products, reflecting an increase of 10% from 2018 and a 5-year CAGR of approximately 8%.

There has been a 76% increase in oncology products over the past five years, and in 2019, oncology products made up 30% of the late-stage pipeline. Growth is primarily due to targeted therapies, which nearly doubled from 2014 to 2019. Gastrointestinal therapies have grown 73% in the past five years and represent 7% of the 2019 pipeline. The gastrointestinal pipeline has seen a significant increase in the percentage of NASH products, growing from 10 products in 2014 to 45 in 2019, as well as growth in products targeting Crohn's and ulcerative colitis.

Central nervous system (CNS) disorders made up 11% of the 2019 pipeline, with an increase of 50% in the number of drugs under development since 2014. Despite the challenges associated with clinical development for CNS disorders, such as a lack of complete disease understanding and sufficient translational animal models, the CNS pipeline added 20 new products in 2019. Despite high-profile failures of Alzheimer's disease products, the CNS pipeline covers a diverse set of indications, from rare neuromuscular diseases to psychiatry to neurodegenerative diseases. In particular, psychiatric products have increased by 27% since 2018 to a total of 29 products.

Infectious disease represents 6% of the 2019 late-state active pipeline, growing 13% over the past five years. Anti-bacterial agents made up approximately 30% of the infectious disease pipeline and represent over 60 products that target gram-positive bacterial infections, pneumonia, and urinary tract bacterial infections, among others. However, there remains a critical unmet need for novel antibiotics to treat antibacterial resistant

Exhibit 9: Number of Late-Stage Pipeline Products by Therapy Area, 2014–2019



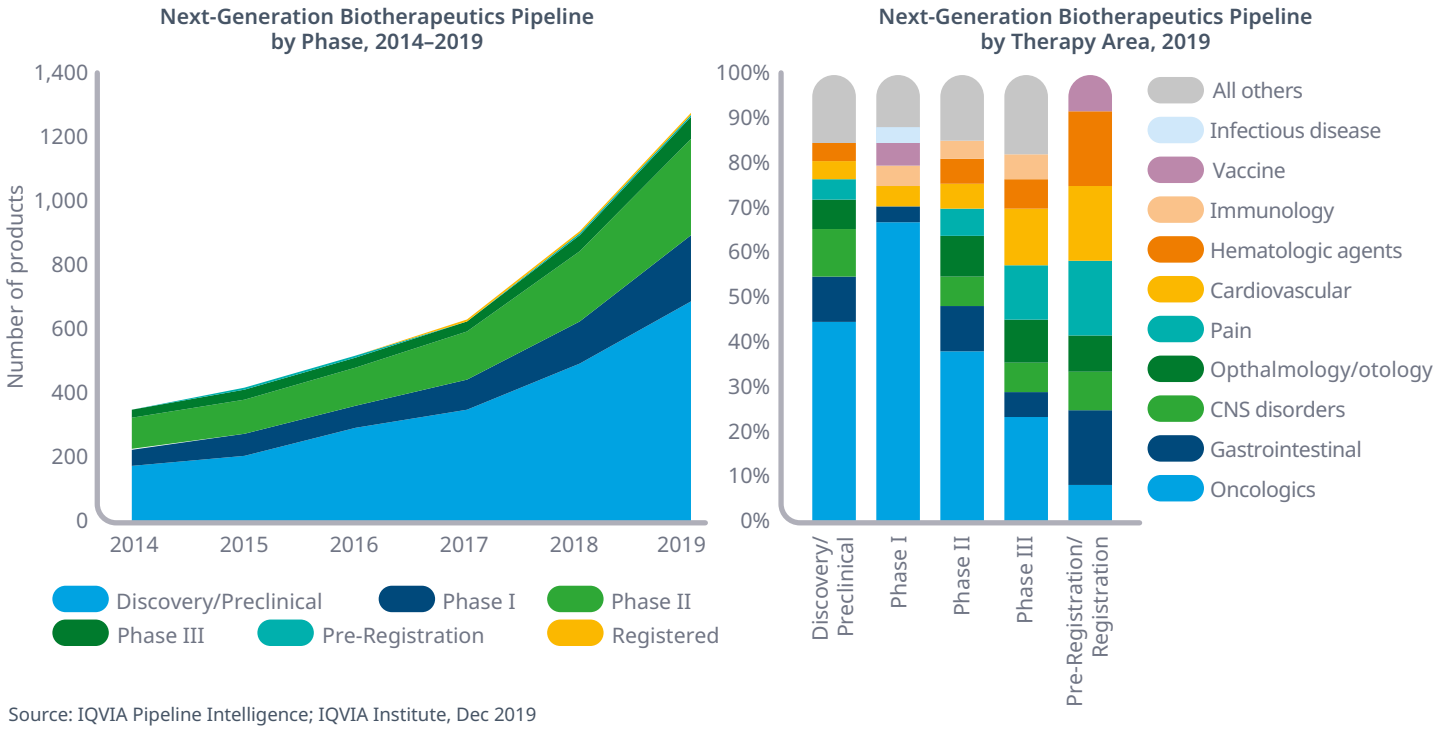
Source: IQVIA Pipeline Intelligence; IQVIA Institute, Dec 2019
Notes: Includes late-stage pipeline, which is defined as active programs (activity in past three years) in Phase II through Registered. Pipeline products are categorized by their most-advanced indication. Additional indications for pipeline drugs still in earlier phases or for already marketed drugs are not counted.

infections; for example, the late-stage infectious disease pipeline contains only four carbapenem-resistant agents, which are antibiotics of last resort. In addition to antibacterial products, the next largest group of agents in the infectious disease pipeline includes antiviral therapies, including three antiviral products for SARS-CoV-2 infection, such as the late-stage compound remdesivir. Of note, the bulk of active compounds in development for COVID-19 are vaccines, and as of March 2020, remain in discovery or preclinical phases of development despite the recent global demand, demonstrating the challenges in aligning priorities for research and development activity that is typically undertaken with very long lead times.

NEXT-GENERATION BIOTHERAPEUTICS

Next-Generation Biotherapeutics (NGB), defined as cell, gene, and nucleotide therapies, now make up nearly 12% of the late-stage pipeline, an increase from 10% in 2018 (see Exhibit 10). Since 2018, 99 products have been added, bringing the total number of products in development to 369. The number of NGB products has more than tripled since 2014, as new pathways for disease treatment and cure command growing attention and investment, especially in previously intractable diseases. Currently, 78% of the late-stage NGB pipeline is in Phase II development, slightly higher than the overall share of Phase II assets in the entire late-stage pipeline (64%). However, the potential for NGBs to receive approval prior to conducting Phase III trials is high, as the FDA has determined that many of these products serve patient populations with critical and urgent unmet needs. Therefore, many of these therapies are potentially closer to commercialization than non-NGB counterparts despite having fewer products in Phase III. Additionally, the pipeline includes predominantly gene therapy and gene-editing technologies, which now comprise 70% of the NGB pipeline, or 278 products. CRISPR technology remains only a minimal part of the late-stage pipeline,

Exhibit 10: Next-Generation Biotherapeutics Pipeline by Phase and Therapy Area Percentage of Total



Source: IQVIA Pipeline Intelligence; IQVIA Institute, Dec 2019

Notes: Next-Generation Biotherapeutics defined as cell and gene therapies or nucleotide therapies with mechanisms including: cell therapy, dendritic cell therapy, NK cell therapy, T-cell therapy, CAR-T cell therapy, CRISPR, T-cell receptor therapy, stem cell therapy, bacterial cell therapy, CIK cell therapy, CIK-CAR therapy, whole cell vaccine, dendritic cell vaccine, bacterial cell vaccine, DNA vaccine, RNA vaccine, exon skipping, nucleic acid-based, gene therapy, oligonucleotide, antisense, RNAi, microRNA mimic, gene editing, CRISPR-Cas9, zinc finger nuclease, RNA therapy, and mRNA therapy.

with only three products in Phase II studies and no others in later developmental stages, despite the great appeal and interest of these products.

NGB late-stage development remains concentrated in several major therapy areas, including oncology, gastrointestinal, hematology, and ophthalmology.

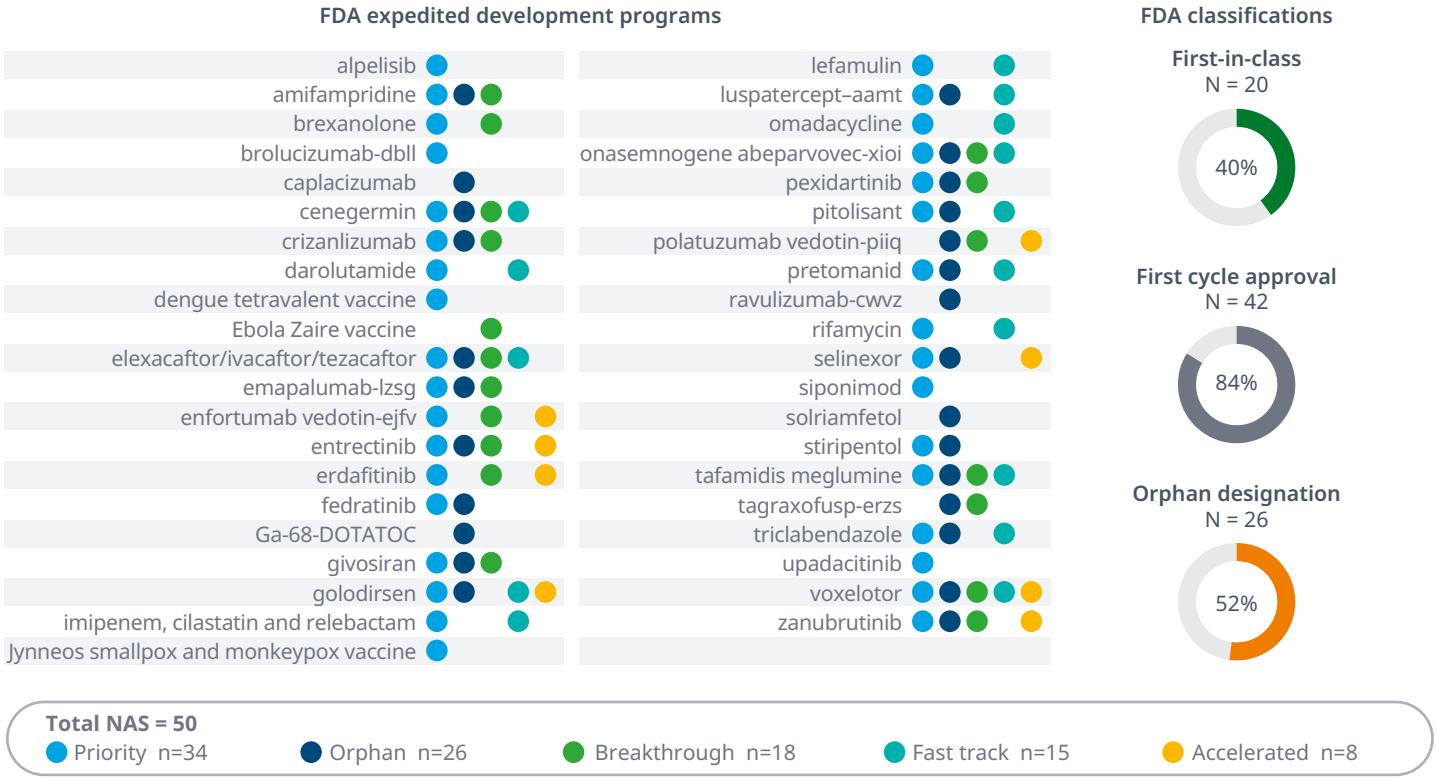
- Oncology continues to hold the largest share of the late-stage NGB pipeline with 128 products, or 35% of the pipeline, after the addition of 31 products in the last year (see Exhibit 10). The growth in this therapy area is due almost exclusively to gene therapies, specifically CAR-T cell therapies, and is expected to continue as off-the-shelf CAR-T therapies become more attractive and developmentally successful. Oncology also includes one of three CRISPR products in late-stage development, an allogeneic CRISPR/Cas9 gene-edited CAR-T cell therapy for the treatment of B-cell malignancies.[26]
- The NGB gastrointestinal late-stage pipeline has also increased and now makes up 9% (35 products) of the NGB late-stage pipeline, including 21 gene therapies in development. These include potentially curative treatments for often fatal diseases in infants and young children, such as mucopolysaccharidosis, Fabry disease, and phenylketonuria.
- In hematology, there are currently 21 gene therapies and/or CRISPR-utilizing treatments in development, with therapies for hemophilia and thalassemia likely to reach commercialization in 2020. Within hematology, there is another late-stage CRISPR product, a gene-edited autologous hematopoietic stem cell therapy for the treatment of beta-thalassemia and sickle cell disease.
- Spurred by the success of voretigene neparvovec (Luxturna) and ease of gene therapy delivery and targeting, ophthalmology continues to be a large area of focus, with 24 gene therapies in late-stage development. The final late-stage CRISPR product in development is a treatment for Leber congenital amaurosis, which usually affects infants and causes severe vision loss.

Despite manufacturing hurdles and questions of treatment durability and patient access, gene therapy and its associated technologies continues to be a major focus of pipeline development, as the potential for curative treatments is perceived to be high.

Next-Generation Biotherapeutics (NGB), defined as cell, gene, and nucleotide therapies, now make up nearly 12% of the late-stage pipeline. The late-stage pipeline for these products remains concentrated in several major therapy areas, including oncology, gastrointestinal, hematology, and ophthalmology.

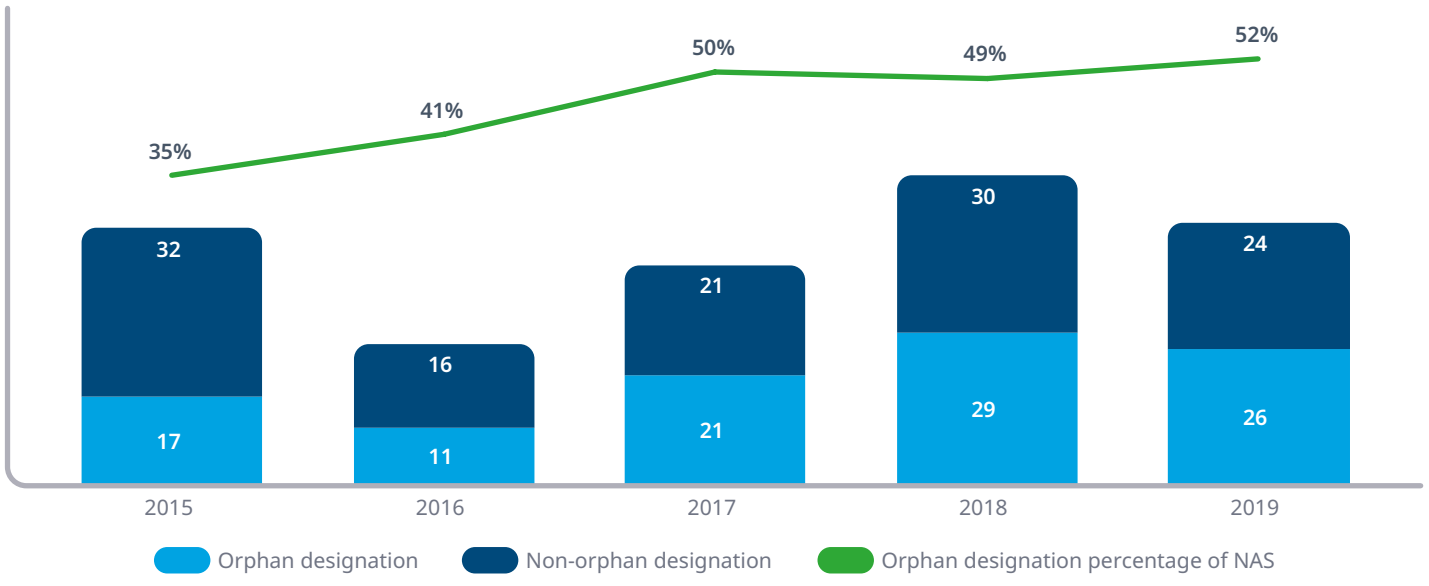
Appendix

Exhibit 11: New Actives Substances (NAS) Launched for the First Time in the United States



Source: IQVIA Institute, Jan 2020

Exhibit 12: NAS Receiving Orphan Designation and Comparison to Non-Orphan Designated NAS, 2015–2019



Source: IQVIA Institute, Jan 2020

Appendix

Exhibit 13: New Actives Substances (NAS) Approved by the FDA Based on RWE

DRUG	TYPE	FDA APPROVAL TYPE	YEAR OF RWE APPROVAL	YEAR OF LAUNCH
lepirudin	natural history cohort	NDA	1998	1998
carglumic acid	natural history cohort	NDA	2010	2010
alglucosidase alfa	natural history cohort	NDA	2010	2006
glucarpidase	natural history cohort	NDA	2012	2012
metreleptin	treatment IND*	NDA	2014	2014
blinatumomab	natural history cohort	NDA	2014	2014
uridine triacetate	natural history cohort	NDA	2015	2016
cholic acid	natural history cohort	NDA	2015	2015
eteplirsen	historic control arm from a registry database	NDA	2016	2016
ivacaftor	post-marketing registry database	sNDA	2017	2012
avelumab	historic control arm from electronic health records	NDA	2017	2017
cerliponase alfa	natural history cohort	NDA	2017	2017
axicabtagene ciloleucel	historical controls from scientific literature	NDA	2017	2017
prucalopride	data included from European health records and claims databases	NDA	2018	2019
migalastat	real world data from the commercial launch of migalastat in Europe	NDA	2018	2018
lutetium Lu 177 dotatate	expanded access protocol	NDA	2018	2018
fish oil triglycerides	natural history cohort	NDA	2018	2018
palbociclib	electronic health records and claims data	sNDA	2019	2015
onasemnogene abeparvovec-xioi	natural history cohort	NDA	2019	2019
entrectinib	external control arm from electronic health records	NDA	2019	2019

Sources: Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: The changing landscape of the regulatory approval process. Pharmacoepidemiol Drug Saf. 2019 Dec 10; Lambda Research Newsletter. 2019 Jul. Available from: https://www.lambda-cro.com/wp-content/uploads/2019/08/Lambda-Research-Newsletter-July-2019.pdf; Pink Sheet. Real-World Evidence: US FDA's Prucalopride Review Shows Datasets' Utility And Limitations. 2018 Oct. Available from: https://pink.pharmaintelligence.informa.com/PS124125/RealWorld-Evidence-US-FDAs-Prucalopride-Review-Shows-Datasets-Utility-And-Limitations; Pink Sheet. Roche Outlines Use Of Real-World Evidence In Entrectinib NDA. 2019 Jun. Available from: https://pink.pharmaintelligence.informa.com/PS125433/Roche-Outlines-Use-Of-RealWorld-Evidence-In-Entrectinib-NDA; FDA. Summary Basis for Regulatory Action. Zolgensma. Accessed Jan 2020. Available from: https://www.fda.gov/media/127961/download; Pink Sheet. How Real-World Evidence Is Playing Out In The Real World. Accessed Feb 2020. Available from: https://pharmaintelligence.informa.com/resources/product-content/sitecore/shell//~/media/informa-shop-window/pharma/2019/files/pdf/how-rwe-is-playing-out-in-the-real-world-webinar-slides.pdf

Notes: *Data collected under a treatment IND or expanded access protocol has been considered a form of RWE by the FDA, such as in rare disease settings where there is little chance of a prospective trial. Does not include: NovoSeven (coagulation Factor VIIa, recombinant), Methylene Blue (methylthioninium chloride), thiotepa, or Risperidone Consta (paliperidone palmitate), as these are not considered NAS.

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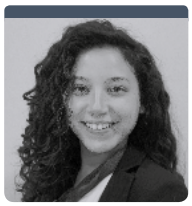

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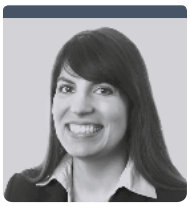
Elyse Muñoz is a Thought Leadership Manager for the IQVIA Institute, managing aspects of IQVIA Institute research projects and conducting research and analysis within global healthcare. Elyse joined IQVIA in 2017 as an associate consultant in the Competitive Intelligence consulting group, where she developed rich clinical and commercial insights to serve clients. She worked in major therapy areas including diabetes, cardiovascular disease and kidney dysfunction, as well as rare diseases such as hemophilia. Elyse holds a Bachelor of Science from Arizona State University in Genetics, as well as a Ph.D. in Genetics from Pennsylvania State University. Her research focused on the genetic makeup of the parasite that causes malaria to aid in the development of targeted drugs to eradicate the disease.



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Notes on sources

This report is based on the IQVIA services detailed below.

IQVIA PIPELINE INTELLIGENCE is a drug pipeline database containing up-to-date R&D information on over 40,000 drugs, and over 9,000 in active development worldwide. The database captures the full process of R&D, covering activity from discovery stage through preclinical and clinical development, to approval and launch.

ARK PATENT INTELLIGENCE is a database of biopharmaceutical patents or equivalents worldwide and including over 3,000 molecules. Research covers approved patent extensions in 52 countries, and covers all types of patents including product, process, method of use and others.

IQVIA PHARMA DEALS is a comprehensive life science deals and alliances database that leverages worldwide information sources to deliver the latest intelligence in deals and alliances.

About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

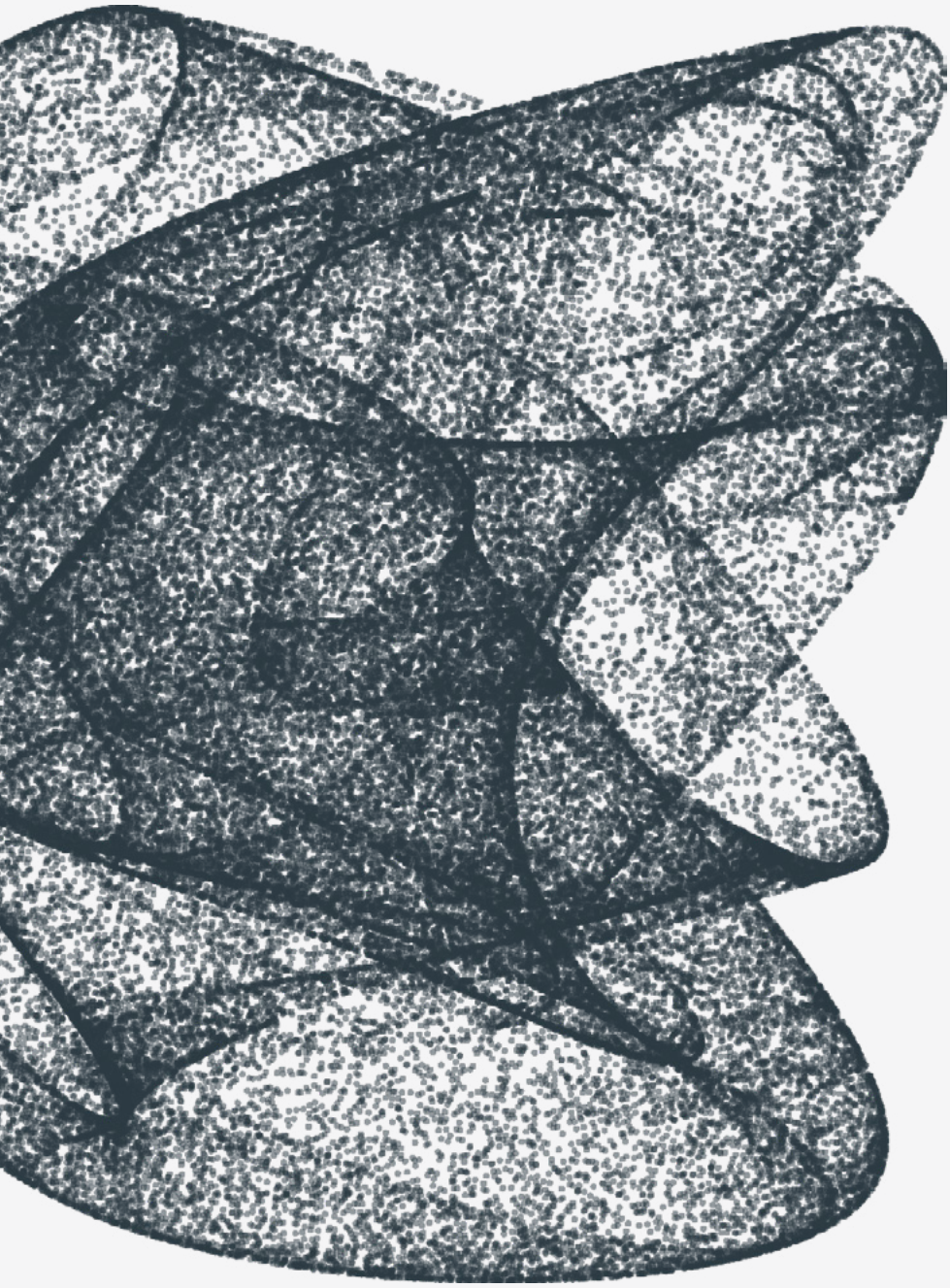
The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding Principles

The Institute operates from a set of Guiding Principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.



The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The artwork on the cover of this research and development achievements report was generated using data collected from IQVIA's Pipeline Intelligence. This data allows the team to analyze the number of successful phase transitions for pipeline products from 2009-2019. This analysis is then used to investigate pipeline products by both phase of clinical development and therapy area.

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