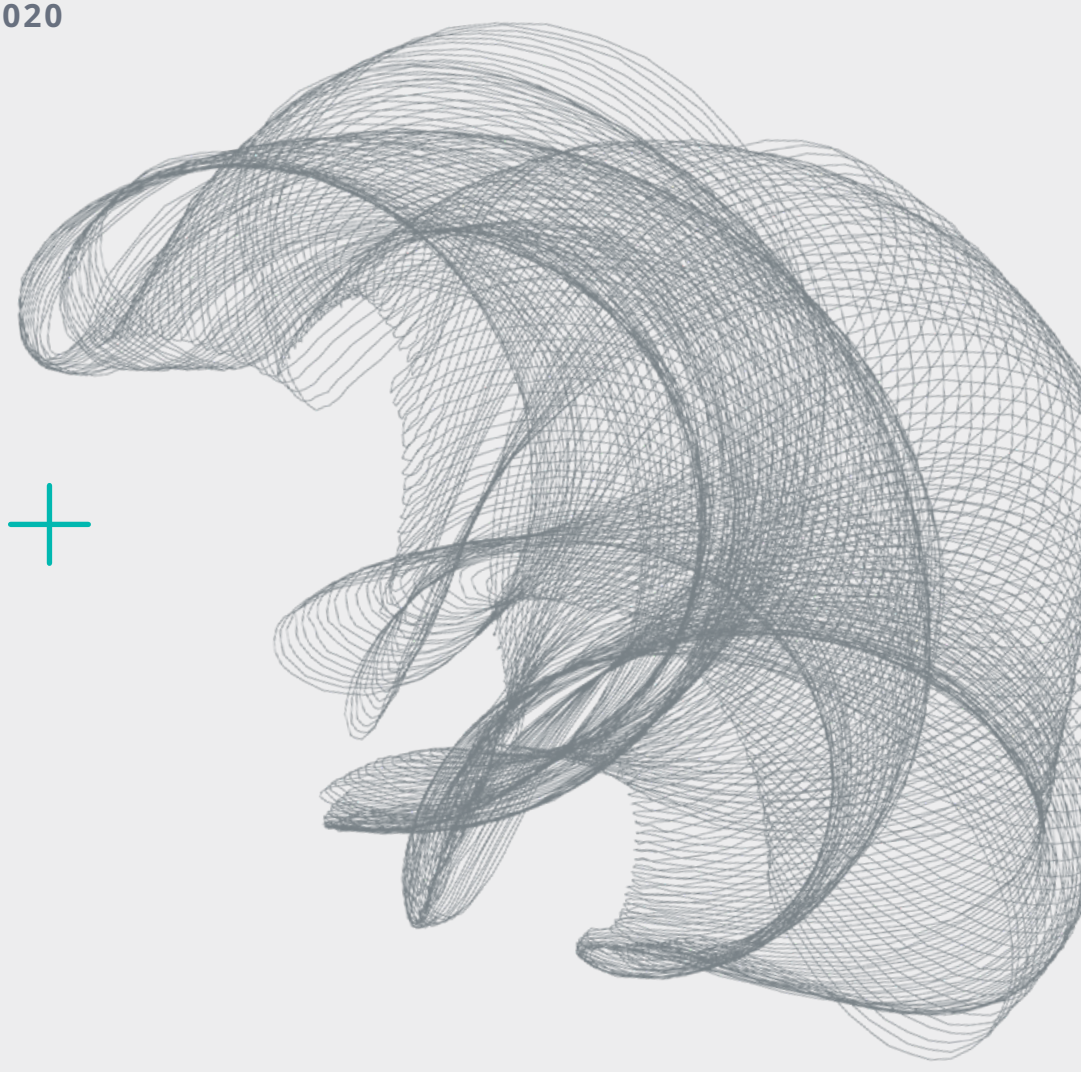
IQVIA INSTITUTE
FOR HUMAN DATA SCIENCE

Global Trends in R&D

OVERVIEW THROUGH 2020



MAY
2021

Introduction

The life sciences innovation system – including hundreds of companies, governments, researchers, doctors, and nurses – adapted to the COVID-19 pandemic in ways large and small. Identifying and genotyping the virus within weeks and developing vaccines which are now reaching millions around the world in less than a year is truly astonishing. And yet this virus is but one disease afflicting patients, and research continues in hundreds of other diseases. Tracking the ongoing efforts of these researchers in this trends report offers a view into their efforts to improve the productivity of this research, to better understand the course of diseases, to optimize processes with technology, and many more exciting developments.

This report assesses the current status in the R&D of medicines at the end of 2020. It provides an analysis of the number of initiated clinical trials, including the impact of the COVID-19 pandemic and COVID-19-specific research. The results of research are compared to the input effort in a Clinical Development Productivity Index. The active pipeline and state of R&D funding are profiled. The record numbers of new active substances (NAS) launched in 2020 are profiled, including where they launched, what types of products they are, and which approval pathways were used.

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, Onil Ghotkar, Priti Girotra, Elyse Munoz, Deanna Nass, Bhagyashree Nawar, John Paul, Urvashi Porwal, Shivika Rastogi, Vaishnavi Shirsath, Durgesh Soni, Benjy Stein, Terri Wallace and dozens of others at IQVIA are gratefully acknowledged.

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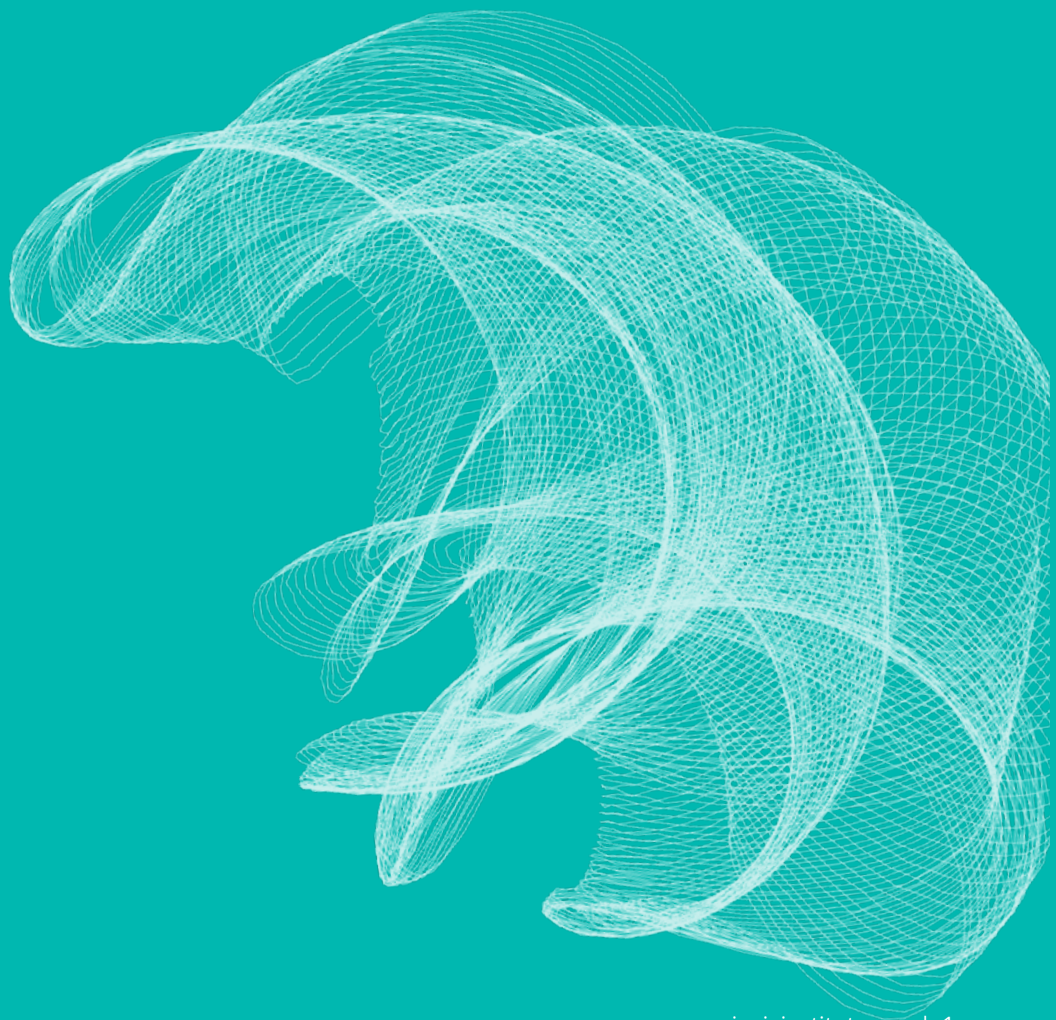
MURRAY AITKEN
Executive Director
IQVIA Institute for Human Data Science

Table of Contents



Overview

In 2020 the COVID-19 pandemic upended life globally and yet not only did research and development activities largely continue – albeit with disruption - they also resulted in vaccines being developed that are already reaching more than 600 million people. The key drivers of these unprecedented results are visible in benchmarks and trends of various aspects of R&D, providing insight into what other improvements are already underway or could be possible.

+ Clinical Trial Activity

Despite significant disruption and reprioritization of clinical trial activity during 2020, activity levels remained historically high (especially in oncology), and the more than 850 interventional industry-sponsored trials for COVID-19 vaccines and therapeutics have yielded 16 approvals to-date and a robust pipeline of additional ongoing studies. Overall, clinical trial starts increased 8% in 2020, similar growth to the prior three years and including the rapid recovery to pre-COVID-19 levels from mid-year. Remote, virtual or decentralized trials increased dramatically in 2020 especially, in trials related to COVID-19, and contributed to the speed of development and authorization of vaccines and treatments. Oncology trial starts in 2020 reached historically high levels, 60% more than were started in 2015, reflecting strong momentum in this area and especially in rare oncology indications, which now account for 63% of total oncology trials. New trial starts in other therapy areas – excluding infectious diseases – fell in 2020 below 2019 levels, reflecting shifting priorities for sponsors and investigators, but in most areas (except respiratory) starts have increased over the past decade. The timelines for the development and approval of COVID-19 vaccines averaged a remarkable seven months from initiation of clinical trials to approval through emergency use authorizations, compared to 9 years and 4 months for the median development time of all vaccines approved in the prior five years.

+ Clinical Development Productivity

The productivity of clinical development – the output relative to the level of effort input – remains historically low as a result of rising trial durations, increased complexity of disease targets and their associated trial protocol designs, and declining success rates. However, productivity rose in 2020, perhaps counterintuitively, as complexity metrics including the numbers of sites and countries included in trials decreased significantly, related to COVID-19 disruptions. The composite success rate across all therapy areas rose slightly to 9.8% in 2020, up from 2019 but still lower than the 10-year average of 12.9%. Each of the productivity elements vary substantially across diseases, with success rates ranging from a high of 32% for rare drugs to less than 10% for vaccines, endocrinology, neurology, and cardiovascular. Rare and oncology trials often take longer to complete than other diseases and are more complex due to eligibility criteria and endpoints.

+ R&D Pipeline

There are more than 5,700 drugs in the early-stage pipeline and over 3,200 in the late-stage pipeline, and while growth in the early-stage pipeline paused in 2020, the late-stage pipeline grew modestly. Total early-stage pipeline products declined by 13% in 2020, the first reduction since 2014, bringing the number of total products back to 2018 levels. In the late-stage pipeline, the number of products increased by 3%,

Clinical trial activity during 2020 continued at historically high levels — especially in oncology — despite significant disruption and reprioritization toward COVID-19 vaccines and therapeutics.

bringing total expansion of the pipeline to 43% since 2015. Oncology drugs reached record high shares with than 40% of the early-stage and more than 30% of the late-stage pipeline. Half of the late phase oncology pipeline is for rare cancers and includes a wide range of next-generation and targeted therapies. Growth in the pipeline of next-generation biotherapeutics stalled in 2020 after almost doubling in the prior two years, but further growth may be expected in the areas of cell and gene therapy and RNA therapeutics.

+ R&D Funding

Funding for early and late-stage R&D increased significantly in 2020, unaffected by the disruptions of COVID-19, and strategic transactions — ranging from M&A through licensing and other forms of collaboration, often between small and large companies — proceeded at typical levels, buoyed by a bolus of COVID-19-related deals. Aggregate R&D expenditures by the 15 companies with the highest pharmaceutical sales reached $123 billion in 2020 and exceeded 20% of sales for the first time, while venture capital flows into the life sciences rose by 50% in 2020 over 2019 levels as interest and valuations in early-stage companies remained at all-time highs. Oncology remains the largest area of deal-activity, consistent with its share of the overall pipeline. Emerging biopharma companies are responsible for 64% of the late-stage pipeline, as more retain control over the development of their innovations. Drugs from China-headquartered companies have risen to 12% of the early-stage pipeline from 2% a decade ago, while European companies have seen their share drop from 33% to 22%.

+ New Drug Approvals and Launches

The total number of first-time global launches of novel active substances (NAS) reached an all-time high of 66 in 2020. Country differences in launches continue, and the U.S. led other countries and remained above 50 for the third consecutive year, reflecting strong growth since 2010 when 25 NASs were launched globally and 24 were launched in the U.S. In the U.S., oncology, neurology and infectious diseases – including COVID-19 vaccines launched under Emergency Use Authorization — made up 73% of total new launches in 2020. There were 31 new orphan drugs – those to treat fewer than 200,000 people – launched in 2020, including 18 first-in-class and 26 approved based on a Phase I or II trial. The time a drug takes to reach patients — measured as the time from patent filing to product launch to a median of 10.7 years in 2020, down from 16.1 years in 2016, and the shortest time since 2002. Emerging biopharma companies originated and launched 40% of NASs in 2020, slightly lower than in the prior two years but significantly higher than historic levels, as more companies remain independent through the development and launch of their innovative medicines.

Clinical development productivity rose in 2020 as complexity metrics including the number of sites and countries in trials dropped and the composite success rate across all therapy areas rose slightly.

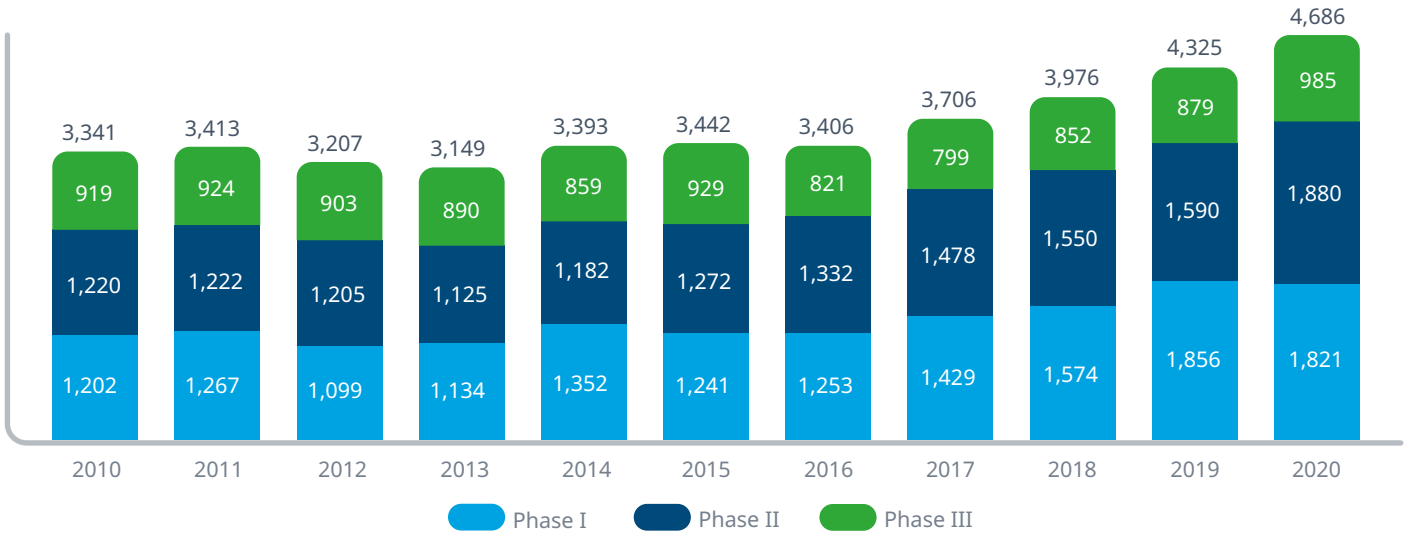
Clinical trial activity

Activity levels for clinical trial activity during 2020 remained historically high (especially in oncology), and the more than 800 interventional industry-sponsored trials for COVID-19 vaccines and therapeutics have yielded 16 approvals to-date and a robust pipeline of additional ongoing studies.

- Clinical trial starts increased 8% in 2020, similar growth to the prior three years, including a recovery after mid-year to higher levels than in 2019 following the immediate disruptions in the second quarter of 2020 — even excluding new COVID-19 trials.
- During the course of 2020, trial starts fell significantly in the first quarter but recovered mid-year to higher levels than in 2019 even without the COVID-19 trials.
- Remote, virtual or decentralized trials increased dramatically in 2020 especially, in trials related to COVID-19, and contributed to the speed of development and authorization of vaccines and treatments.
- Oncology trial starts in 2020 reached historically high levels, 60% more than were started in 2015, reflecting strong momentum in this area and especially in rare oncology indications, which reflect the movement toward precision medicine and now account for 63% of total oncology trials.
- New trial starts in other therapy areas — excluding infectious diseases — fell in 2020, reflecting shifting priorities for sponsors and investigators, though most areas (except respiratory) remained at historically high levels.
- A surge of COVID-19 related activity for novel therapeutics and vaccines, including reuse of approved medicines, resulted in more than 800 interventional industry-sponsored studies initiated during over the past year, yielding 12 vaccines and 4 novel therapeutics to date.
- The timelines for the development and approval of COVID-19 vaccines averaged a remarkable seven months from initiation of clinical trials to approval, substantially faster than the average of nine years and four months for other vaccines approved in the prior five years.
- Clinical trials continue for 65 previously approved molecules, reflecting the breadth of effort underway to find effective therapeutics for COVID-19.

Total clinical trial starts increased 8% in 2020 as the industry adapted quickly to shifting priorities and logistical challenges

Exhibit 1: Total Number of Clinical Trials by Phase 2010–2020



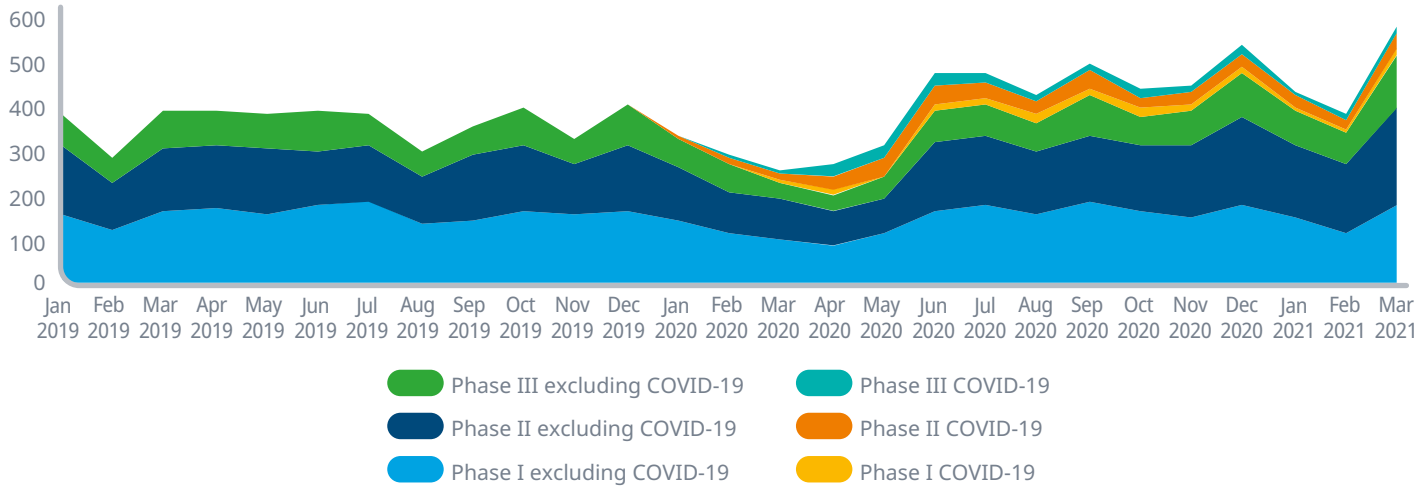
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- Overall clinical trial activity rose 8% in 2020, the fourth consecutive year with an increase above 7%.
- Many of the most active disease areas such as oncology and rare diseases continued to increase numbers of new trials and were less affected by disruptions from COVID-19.
- While the intention to start trials continued with relatively small disruption, the operation of trials — including recruiting patients and completing studies — may have been disrupted differently and these trends should be interpreted with caution.

Exhibit 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, interventional trials and device trials were excluded.

Monthly clinical trial starts declined significantly in early 2020 but recovered from June to higher levels than in 2019

Exhibit 2: Clinical Trial Starts by Month and Phase Jan 2019–Mar 2021



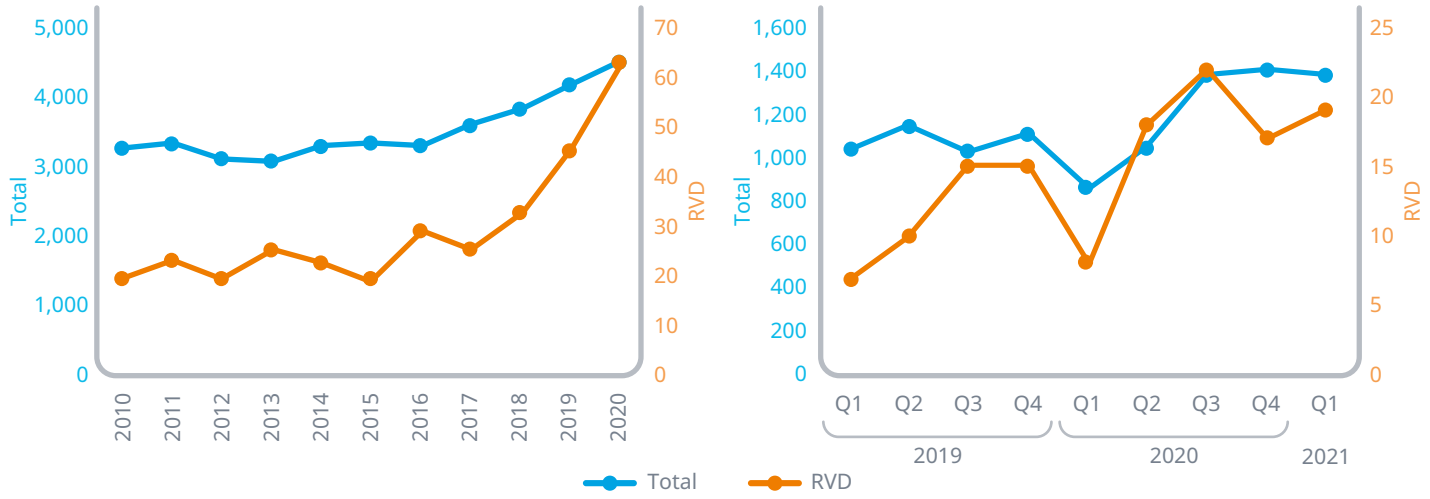
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- During the course of 2020, monthly trial starts fell significantly in the first quarter but recovered from mid-year to higher levels than in 2019 even without the COVID-19 trials.
- Notably as second and third waves of COVID-19 cases have persisted, these have largely not resulted in parallel disruptions to trial starts, perhaps as the adaptations and adjustments made by hospitals, investigators and sponsors were able to continue operations despite the pandemic.
- While there has been a rebound in trial starts, the overall capacity of sponsors and investigators to conduct trials, along with continued reduced patient volumes in health systems, may be contributing to lower numbers of trial starts.
- Additionally, more recent trial starts are disproportionately planned start dates as opposed to actual, and capacity and patient numbers will be a limiting factor on both starts and ongoing operations.
- The unprecedented reallocation of resources to COVID-19 trials is visible here as a sustained wave of trials that began early in the pandemic and have continued, including both novel agents and trials to assess utility of existing agents for COVID-19 treatment or symptoms.

Exhibit 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, interventional trials and device trials were excluded.

Trials which are remote, virtual, or decentralized have been increasing and accelerated during the COVID-19 pandemic

Exhibit 3: Trial Starts for All Trials and Remote, Virtual or Decentralized Trials (RVD)



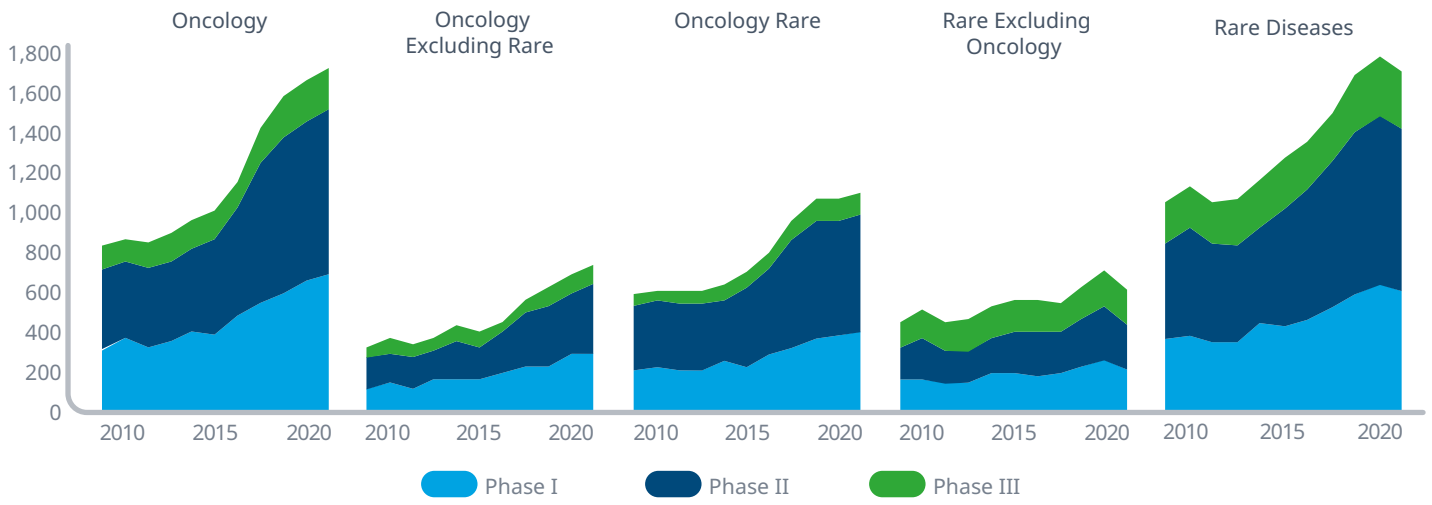
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- Clinical trials with design or operation features that allow remote, virtual or decentralized operations and interactions with 65 trials started in 2020, double the 2018 level.
- All growth in these types of trials was a result of COVID-19 related trials which, by necessity, must be handled differently.
- The need to generate consistent, regulatory-quality clinical data with large trial populations, reduced enrollment times and near-real-time insights across geographies while also protecting patients and investigators from unnecessary risks prompted the adoption of these decentralized approaches.
- COVID-19 trials offer a dramatic illustration of how the assumed years-long process to develop a vaccine can be optimized and bring potential for other trials to be accelerated or improved in the future, especially because before the last year, there has been systemic reticence to use these approaches and a preference for traditional in-person trials.
- Quarterly starts for non-COVID-19 dipped in the first quarter of 2020 for trials overall as well as for these more flexible trials, as the COVID-19 pandemic had an impact on all types of operations, even if less dramatic for remote, virtual and decentralized trials.
- During COVID-19, these remote features have enabled some trials to start when others might not have been able to, enroll more rapidly, or conduct longer term monitoring studies with less burden on providers and patients.

Exhibit Notes: Trials which have a number of decentralized features often don't disclose those in trial registry information, and trials were identified as remote, virtual or decentralized based on a selection of words and phrases included in the trial description, design or notes and reflect an imperfect guide to trends in these trials. Some attributes considered are the use of words, phrases and synonyms as well exclusions for false positives. Generally, terms were similar to telemedicine, remote visits, use of remote sensors, or that the trial is noted to be remote, decentralized, siteless, virtual, or using the increasingly common use of electronic informed consent. In some cases central, remote or distributed are part of common medical terms associated with diseases and are unrelated to the trial design and were excluded.

Oncology trial starts reached historically high levels in 2020, up 60% from 2015 and mostly focused on rare cancer indications

Exhibit 4: Clinical Trial Starts by Year 2010–2020



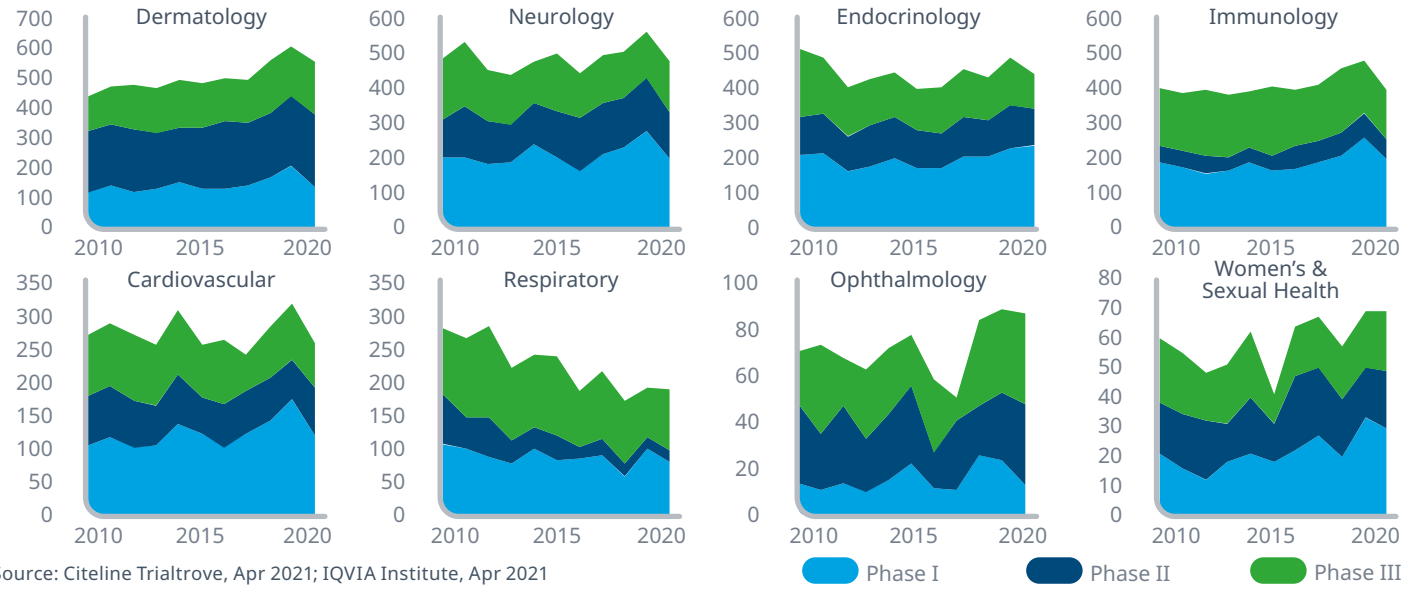
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- Oncology and rare diseases are two of the largest areas of clinical trials, and both represent areas less disrupted by COVID-19 than others.
- Oncology trial starts in 2020 reached historic high levels, 60% more than started in 2015, reflecting strong momentum in this area.
- The overlap between oncology and rare diseases is significant, with rare oncology trials representing 63% of oncology and 64% of rare trials in 2020.
- Trial starts in these diseases continued historic trends in trial initiations, except for some rare diseases outside oncology.
- While patients with rare diseases are more often immune-compromised than other diseases or have other health risks, factors noted to be at higher risk from COVID-19, this has not resulted in delays to trial starts as much as it has in other diseases.

Exhibit 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, interventional trials and device trials were excluded.

Clinical trial starts in other important disease areas declined slightly in 2020, though remain high in most cases

Exhibit 5: Industry Sponsored Interventional Trials by Start Date 2010–2020



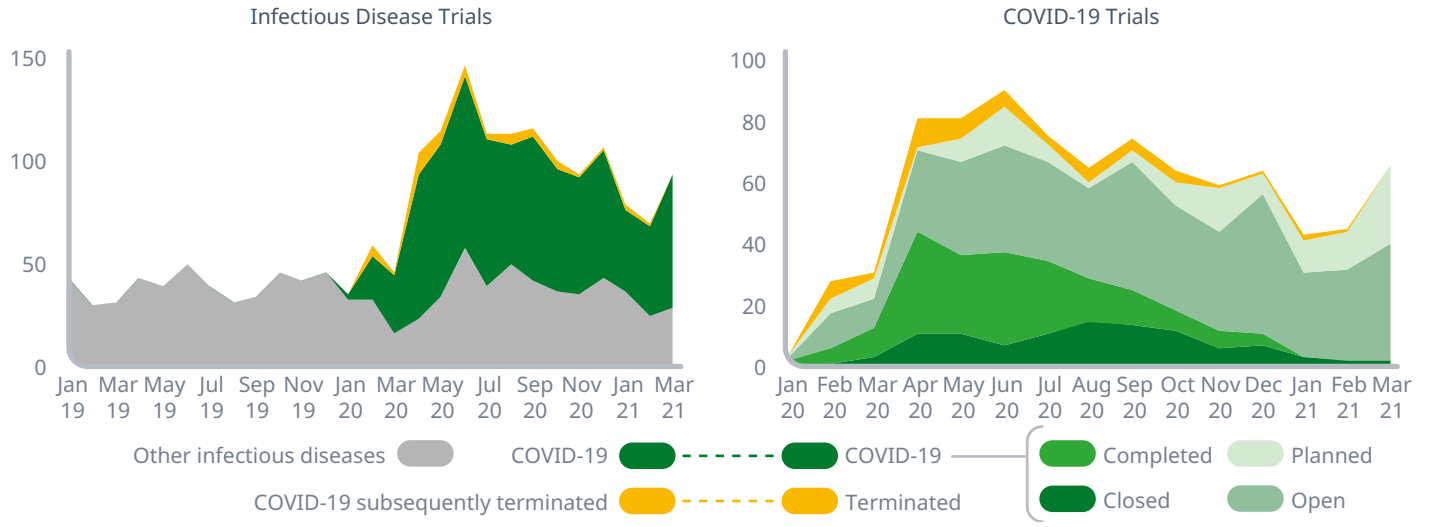
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- Across many disease areas, the rising number of trials over the past 10 years paused or reversed in 2020 due to disruptions from COVID-19.
- More of the declines were in Phase I trials, as initiating new human trials during the pandemic presented difficulties for sponsors and investigators.
- In most cases, however, the number of trial starts was at or above the 2018 level and represented only temporary disruptions to activity.

Exhibit 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, interventional trials and device trials were excluded. Disease definitions not mutually exclusive.

A surge of activity focused on COVID-19 vaccines and therapeutics resulted in 850+ industry-sponsored interventional trials

Exhibit 6: Infectious Disease Clinical Trial Starts by Month January 2019–March 2021



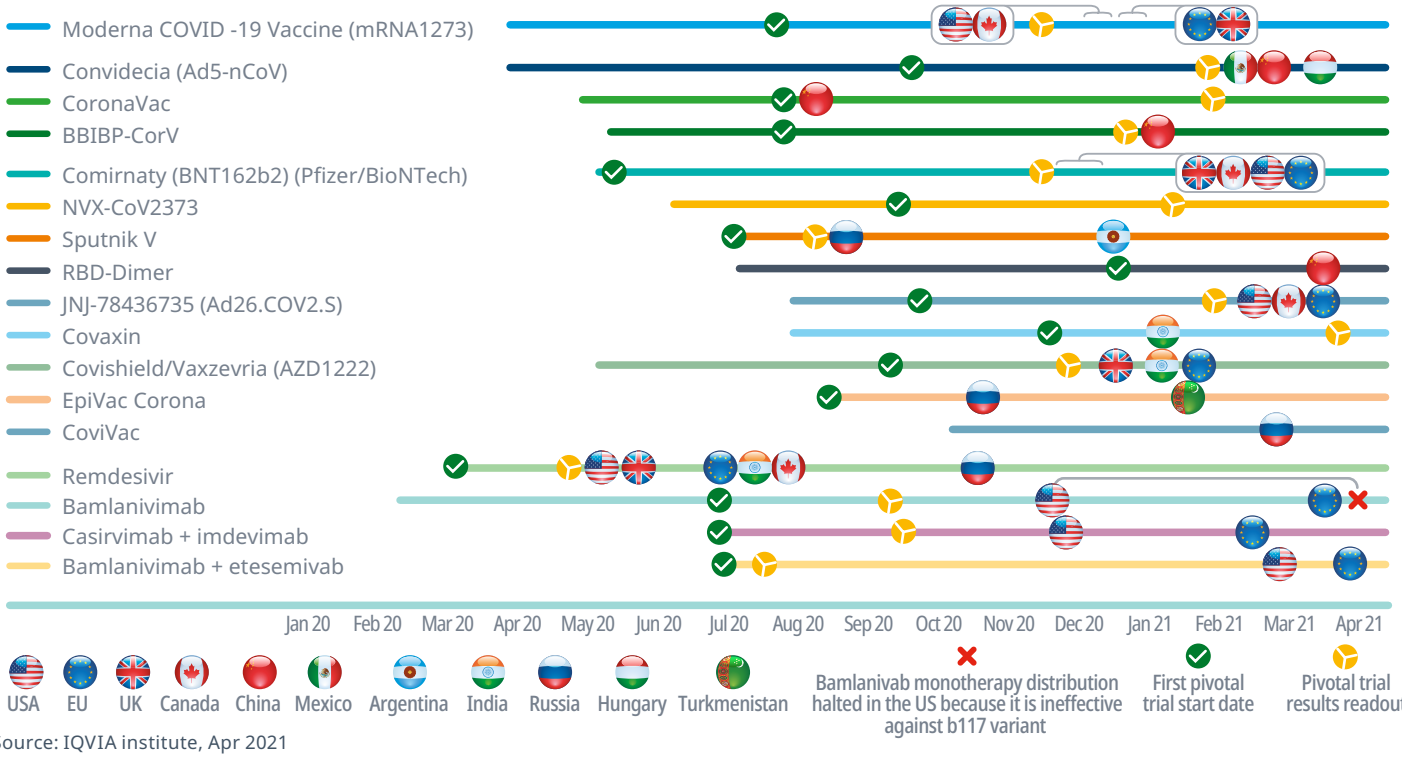
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021

- A surge of COVID-19 related activity for novel therapeutics and vaccines, including reuse of approved medicines, resulted in 866 interventional industry-sponsored studies initiated since the beginning of 2020, yielding 12 vaccines and 4 novel therapeutics to date.
- Of the trials started, 51 were subsequently terminated, typically for having no positive effects.
- The remaining 815 active COVID-19 trials represent 61% of infectious disease trials started from 2020 through early April 2021.
- Other infectious disease trial initiations were down 7% in 2020 compared to the prior year across all phases.
- Overall, 49% of COVID trials remain active, 15% are planned but not active, 30% are either closed or completed presumably pending publication of results.

Exhibit Notes: COVID-19 Trials include vaccines, therapeutics, and existing medicines being studied for COVID-19 if they started during this period.

The global efforts focused on COVID-19 yielded rapid development and approval of 12 vaccines and 4 new therapeutics

Exhibit 7: Timelines of Global COVID Vaccines and Therapeutics Trials and Their Authorization for Emergency Use/Approval by Country



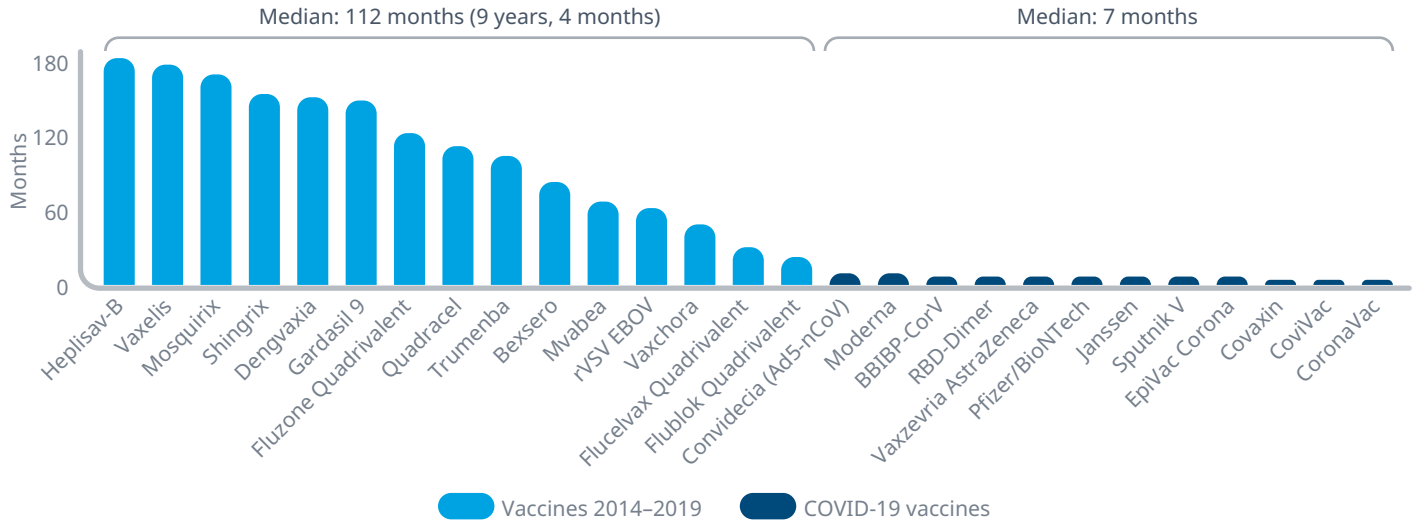
Source: IQVIA institute, Apr 2021

- Globally, 12 vaccines and 4 novel therapeutics for COVID-19 have been developed and approved all in less than a year, with variations in the specific authorizations and timing.
- All of these novel treatments have been approved through emergency use authorizations, demonstrating regulatory flexibility in the face of the global pandemic, and ensuring that the vaccines and treatments reach patients as quickly as possible.
- Some of the vaccines are available only in the country they were developed or in geopolitically aligned locations, while others are more widely and globally available.
- As a result, in the wake of this unprecedented pace of development and authorization, it is estimated that over 600 million people have been vaccinated to-date, raising the real possibility of achieving global vaccination levels consistent with 'herd immunity' by the end of 2022.
- Vaccines alone will not help patients with the virus, and treatments are required for COVID-19, especially to manage the complex symptoms and complications and intermittent flare-ups previously infected patients may experience, as well as those patients who are infected with a viral variant even if vaccinated, all issues expected with an endemic virus.
- Therapeutics for COVID-19 have also had unprecedented speed to patients. Some of the treatments were in development for other conditions prior to testing in relation to COVID-19, which included having testing volumes already on-hand, and aided the rapid start of their trials for COVID-19.

Exhibit Notes: Each line starts at the first clinical start date. Country flags indicate date of emergency use authorization/approval. Selected country/region authorizations shown. Vaccines are being administered globally in more than 100 countries representing over 95% of the world's population.

COVID-19 vaccines were developed and approved in an average of 7 months compared to 9 years and 4 months for other vaccines

Exhibit 8: Time (in months) from a Vaccine's First Clinical Trial Start to First Authorization



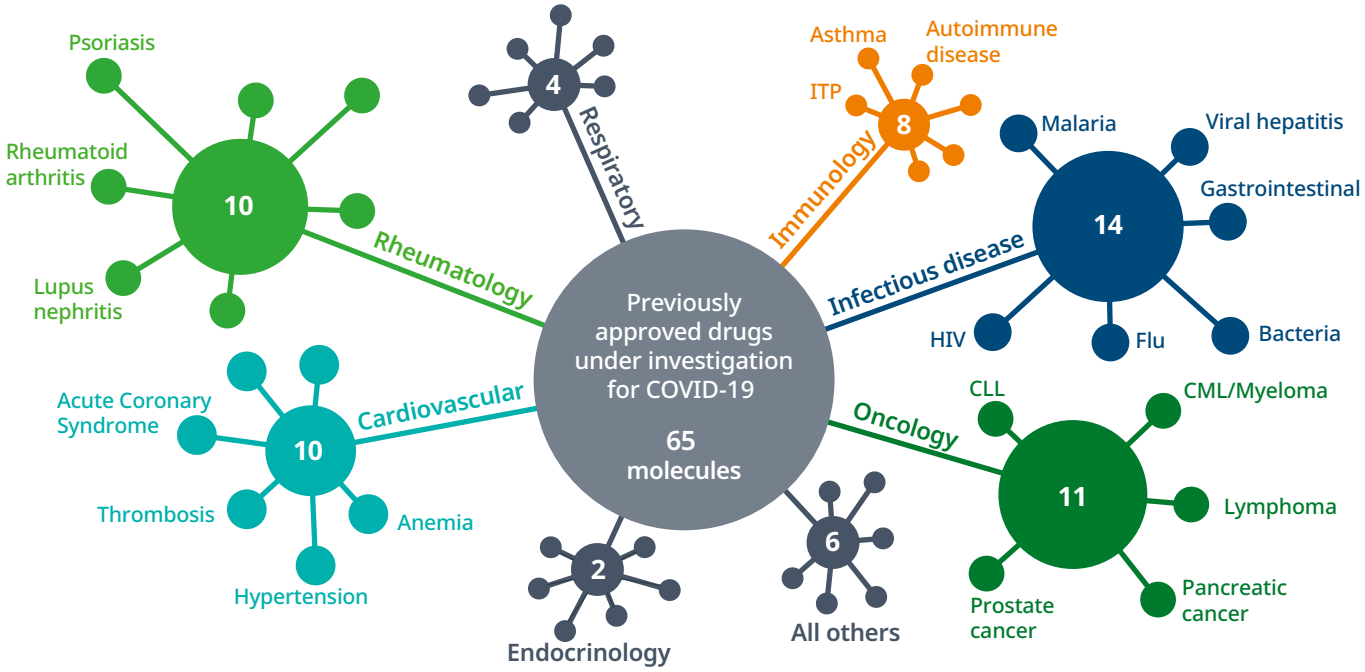
Source: IQVIA Institute, Apr 2021

- Globally as of April 9, there were 12 vaccines approved anywhere in the world for COVID-19, all via emergency use authorizations with a median of 7 months elapsed between the start of the first trial globally and the first authorization in any country, compared to 9 years, 4 months for non-COVID-19 vaccines in the prior five years.
- The time elapsed from trial start to reaching patients includes steps in typical trial and approval sequence, including study treatment durations, post-treatment observation periods and follow-up tracking, as well as periods for analysis, management decision-making, regulatory reviews, scaling up manufacturing and negotiating with purchasers.
- COVID-19 vaccines had a median patient treatment duration in the study designs of 7 months with several tracking patients up to a year after vaccination, taking the study period beyond the emergency use authorization in most cases. This is compared to a median 11 months in non-COVID trials, all of which had other aspects of the development sequence substantially extend their time to market.
- In the five years to 2019, new vaccines have taken as little as 23 months and as long as 15 years and 2 months with a median of 9 years and 4 months, none of them receiving an emergency use authorization.
- The pace of COVID vaccine development could not be more timely, as many countries are still experiencing significant and surging outbreaks.
- As a result of these rapid approvals and government actions around the world, vaccinations have started in countries with at least 95% of the world's population.

Exhibit Notes: Time measured in months from the start of the first trial of any phase and the first approval of any type globally (including emergency use authorizations if applicable). All vaccines launched globally from 2014-2019 and COVID-19 vaccines approved to date as of April 9, 2021.

COVID-19 trials continue for 65 previously approved molecules, reflecting the breadth of effort underway to find effective therapies

Exhibit 9: Currently Marketed Medicines by Disease and Indication Undergoing Research for COVID-19



Source: IQVIA Pipeline Intelligence; IQVIA Institute, Feb 2021

- While relatively few existing medicines have been shown to have benefits for COVID-19 patients in the trials completed so far, more than 60 previously approved medicines for other diseases were involved in trials to assess their efficacy for COVID-19 infections or associated symptoms.
- As disease etiology and viral biology were explored and became better understood through early 2020, products with known or hypothesized effects on similar viruses or downstream bodily responses, such as cytokine storms, entered the clinic.
- Often the mechanism of action was thought to be similar to or acting in ways that would benefit patients with symptoms.
- Many antibody treatments that typically treat inflammation were investigated for the aspects of cytokine storm or immune over-response some patients were experiencing.
- The previous approval of these products allowed several products to move straight into Phase III development, allowing patients to enroll quickly and receive potentially life-saving treatments when no other options were available.
- Some of these medicines were used off-label prior to the completion of trials, and while the number of medicines entering research was unprecedented in speed, it was in many ways too slow for the needs of providers and patients.

Exhibit Notes: Medicines with a highest research phase of marketed with new COVID-19 research underway as of Dec 31, 2020.

Clinical development productivity

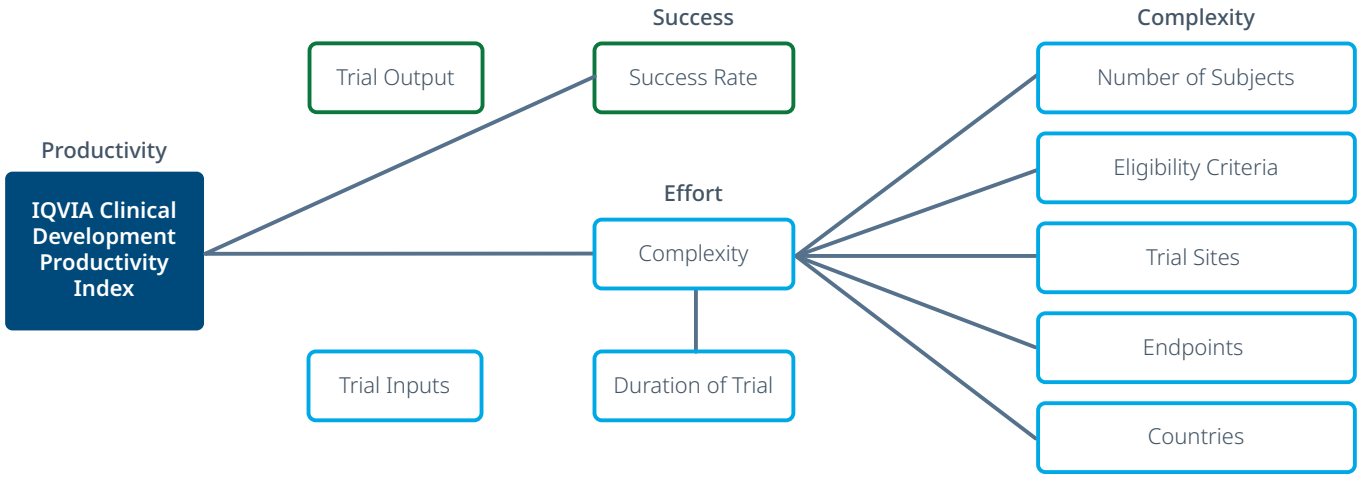
Clinical development productivity remains historically low as a result of rising trial durations, complexity of disease targets and their associated trial protocol designs, and declining success rates.

- Clinical development productivity – a composite metric of success rates, clinical trial complexity and trial duration – rose in 2020 after a decline in 2019 but remains equivalent to 2018, and the last five years average an index of 18 compared to 21 in the prior five years.
- The composite success rate across all therapy areas was 9.8% in 2020, up from 2019 but still lower than the 10-year average of 12.9%.
- Clinical development success rates vary widely by therapy area, from a high of 32% for rare drugs to less than 10% for vaccines, endocrinology, neurology, and cardiovascular.
- Clinical trial complexity has been rising since 2010 but dropped from a peak in 2018, and now is about 6% above the level observed 11 years ago.
- Trial durations have been rising across all phases and average 1.5 years in Phase I, 2 ¾ years in Phase II and 2.5 years in Phase III. As measured from trial start to primary completion.
- The composite Clinical Development Productivity Index rose in 2020 after having declined since 2015 but productivity remains historically low as success rates continue below average and the complexity of trials continues to rise.

The composite Clinical Development Productivity Index rose in 2020 after having declined since 2015, but productivity remains historically low as success rates continue below average and the complexity of trials continues to rise.

A Clinical Development Productivity Index provides a composite metric of success rates, clinical trial complexity and trial duration

Exhibit 10: Clinical Development Productivity Index

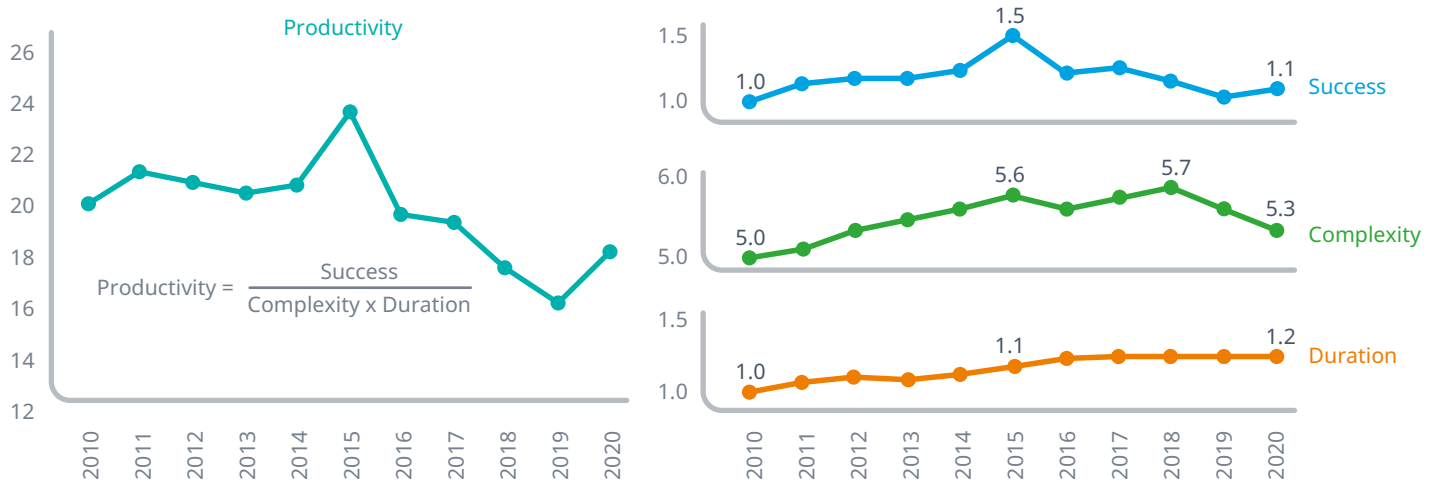


Source: IQVIA Institute, Apr 2021

- The productivity of the clinical development process can be considered as a measure of trial outputs (drugs, innovation, trial success, etc.) compared to a measure of trial inputs or resources dedicated to obtaining those outputs (e.g., aspects of trial complexity, duration, monetary investments, etc.). Such measures of success, complexity and trial duration were selected for inclusion in the productivity index as described above.
- Increases in success will increase productivity overall as will decreases in complexity or duration. Conversely, decreases in success will drive down the productivity index, as do increases in complexity and duration.
- To obtain current-state measures of trial complexity (mean number of endpoints, sites, countries, patients, eligibility criteria), as well as data on trial duration, attributes were leveraged from Citeline Trialtrove clinical trial database. In order to determine the number of eligibility criteria and endpoints from the unstructured or semi-structured text in trial records, IQVIA's Linguamatics natural language processing (NLP) platform was used to identify common formatting patterns employed by trial sponsors in detailing these features. Success metrics were calculated from IQVIA™ Pipeline Intelligence based on medicines progressing a subsequent research phase or being discontinued, suspended, withdrawn or becoming inactive for three or more years (see Methodology). Each metric in each phase for each disease is indexed to the equivalent 2010 value for all diseases. Indices are available for each phase or as an average across phases.
- An analysis of productivity was conducted across all trials started between 2010 and 2020 with details included for therapy areas: cardiovascular, dermatology, infectious diseases, endocrinology, immunology, neurology, oncology, respiratory, and vaccines (separately from infectious diseases), and rare diseases.

Clinical development productivity increased in 2020 though remains historically low due to longer trials and greater complexity

Exhibit 11: Clinical Development Productivity Index and Elements of Productivity Indexed to 2010 Values



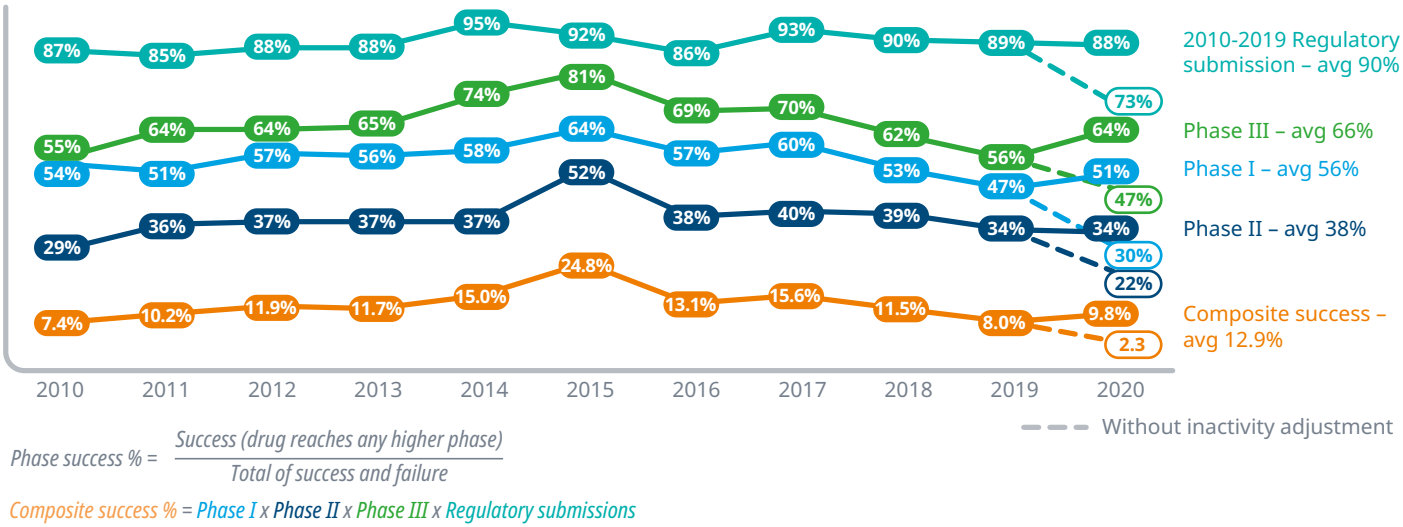
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021; IQVIA Linguamatics, Apr 2021

- Clinical development productivity — a composite metric of success rates, clinical trial complexity and trial duration — rose in 2020 for the first time in five years as complexity was reduced and the success rate, adjusted for pandemic-related inactivity, increased slightly.
- Success rates increased from 8% in 2019 to 9.8% in 2020 when adjusted for unusually high numbers of drugs inactive for more than three years, likely related to the COVID-19 pandemic.
- Without the inactivity adjustment, composite success rates would have declined to 2.3% in 2020, despite relatively consistent absolute numbers of positive phase progressions in all phases.
- Complexity as a composite measure of attributes of trials that make them more difficult to conduct declined in 2020, but the complexity decrease is linked to the reduction in trial countries and sites for 2020 trial starts, likely linked to disruptions from COVID-19.
- The duration of trials is understood to be generally rising as research shifts to oncology and rare diseases, where trials take longer to recruit for and conduct. As these analyses are based on the year trials start, more recent starts which have already completed skew the results and require adjustment to reflect the true trend.

Exhibit Notes: Success rates and durations are indexed to the mean value for all diseases in 2010 equal to 1. The five complexity metrics are indexed to all diseases in 2010 equal to 1, and then summed, equaling 5.

The composite success rate across all therapy areas was 9.8% in 2020, up from 2019 but still lower than the 10-year average of 12.9%

Exhibit 12: R&D Composite Success Rate and Average Phase Success Rates Phase I to Filing, 2010–2020



$$\text{Phase success \%} = \frac{\text{Success (drug reaches any higher phase)}}{\text{Total of success and failure}}$$

Composite success % = Phase I x Phase II x Phase III x Regulatory submissions

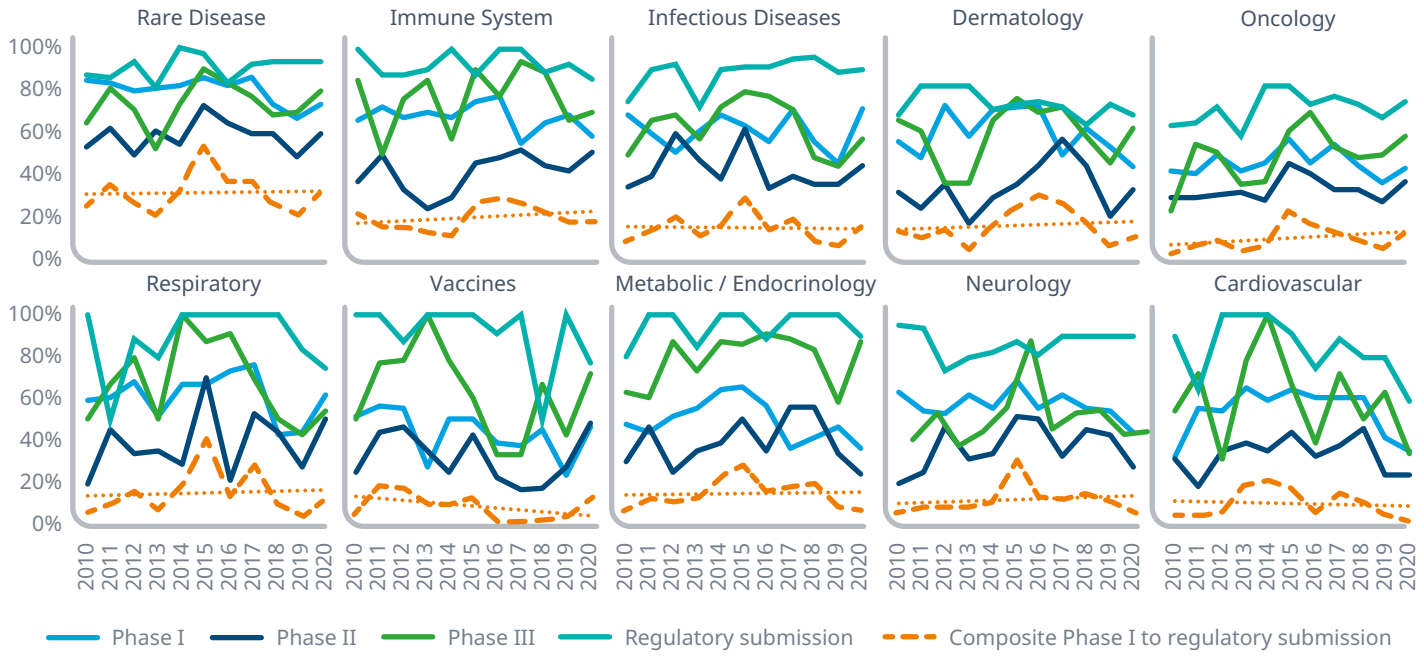
Source: IQVIA Pipeline Intelligence, Feb 2020; IQVIA Institute, Feb 2021

- With information available to date, average success rates dropped in 2020 by 10–15% across various phases, but if historic numbers of failures were to have continued, overall success rates would have risen slightly, and the composite rate would have risen over 2019.
- The events of 2020, associated with COVID-19, appear to have paused or delayed several trials past the three-year threshold used to infer inactivity, and thus are considered failures.
- Any update of information from a trial sponsor is an indication of ongoing research, and as most companies do not announce every failure, using an absence of updates to infer inactivity is critical to assessing probability of success.
- It is possible that after the disruptions of 2020, trial activity will return to normal and some of these inactive trials will restart and no longer be considered 'failed,' resulting in a restatement of the 2020 results.

Exhibit Notes: Phase success rates are calculated as the percentage of products reaching a subsequent phase in the year out of the total of products with a an outcome including those which are discontinued, suspended or withdrawn as well as those which have been inactive for three years. The date three years after the last update determines which year the drug is considered to have gone inactive and become included in the denominator of the success rate.

Across disease areas, 2020's composite success rate was below the 10-year trend except for vaccines and infectious diseases

Exhibit 13: R&D Phase and Composite Success Rates by Therapy Area in 2010–2020



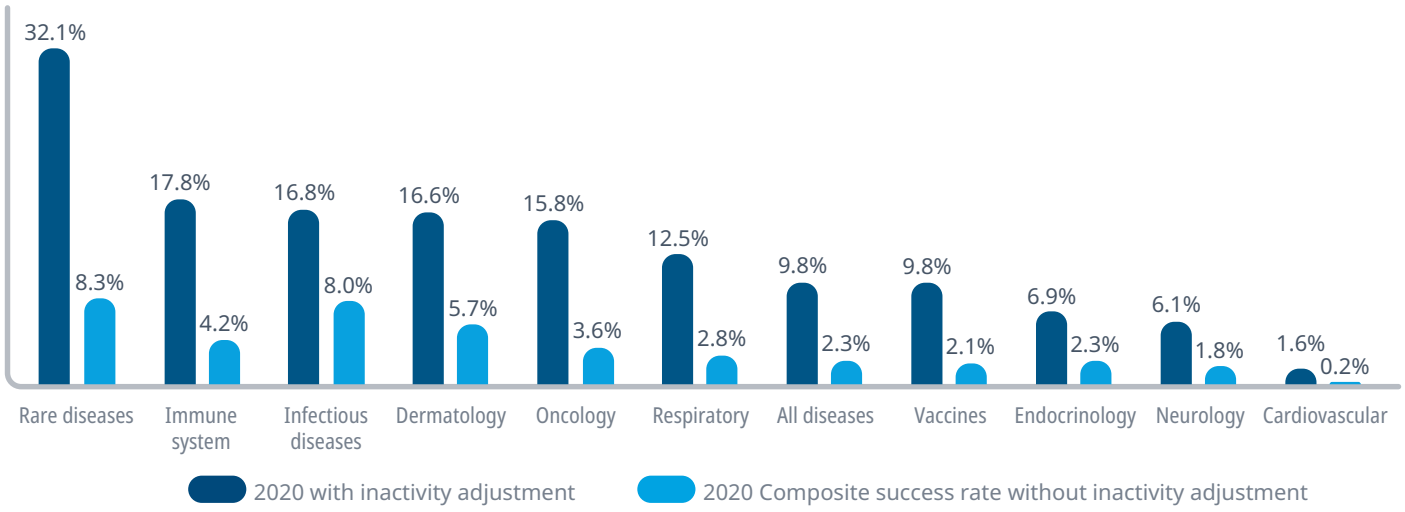
Source: IQVIA Pipeline Intelligence, Mar 2021; IQVIA Institute, Mar 2021

- Across therapy areas, 2020's composite success rate was lower than the 10-year trendline in all classes except for vaccines and infectious diseases.
- Therapy area composite success rates are extremely different and range from 32% for rare diseases to less than 10% for endocrinology, neurology, and cardiovascular.
- Vaccines had a very successful 2020, thanks to COVID-19 trials, reversing a four-year trend of composite success rates below 3%.
- Sharp changes in 2020 were otherwise relatively absent and no repeat of 2015's outlier successes in neurology, respiratory, oncology and rare diseases, which contributed to an industry high that year and powered the subsequent emergence of new medicines in these disease areas over the years since.

Exhibit Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Infectious diseases excludes vaccines.

Probability of success varies considerably across diseases even as 2020 represents an extremely unusual year

Exhibit 14: R&D Composite Success Rate by Therapy Area in 2020 and Scenario Based on Historic Failure Rate Data



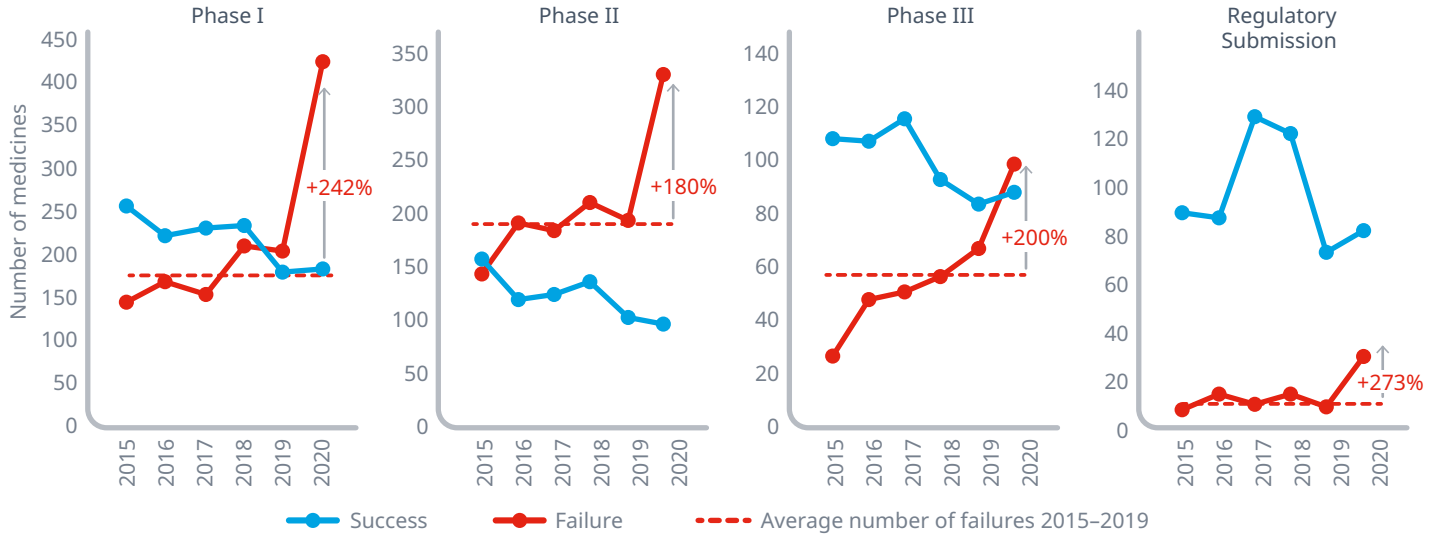
Source: IQVIA Pipeline Intelligence, Mar 2021; IQVIA Institute, Mar 2021

- The probability of success in 2020 across key diseases remains significantly varied with rare diseases achieving an unusually high 32% as a range of genomics and precision medicine tools are increasingly aiding rare disease development, especially in cancer.
- Notably, the inactivity observed across the industry in 2020 reduced the estimated rare disease success rate by almost 75% to only 8.3% when considering unadjusted results.
- Research for drugs for the immune system, those for a range of autoimmune disorders, had a 17.8% composite success rate in 2020, down slightly from 2019.
- Infectious disease drugs had a 16.8% composite success rate, above the rate of 9.8% for all diseases and including a range of antivirals, antibacterials and antiparasitics, and have seen a rising level of investment as research into neglected tropical diseases continues to grow.

Exhibit Notes: The alternative scenario presented is one where the average number of failures per year in 2015 to 2019 is included in the calculation of 2020 successes in place of the observed failures in 2020.

Disruptions to trial progressions resulted in significant increases in inactive records, which are not expected to continue as failures

Exhibit 15: Success or Failure of Medicines to Progress to a Subsequent Research Phase, 2015–2019



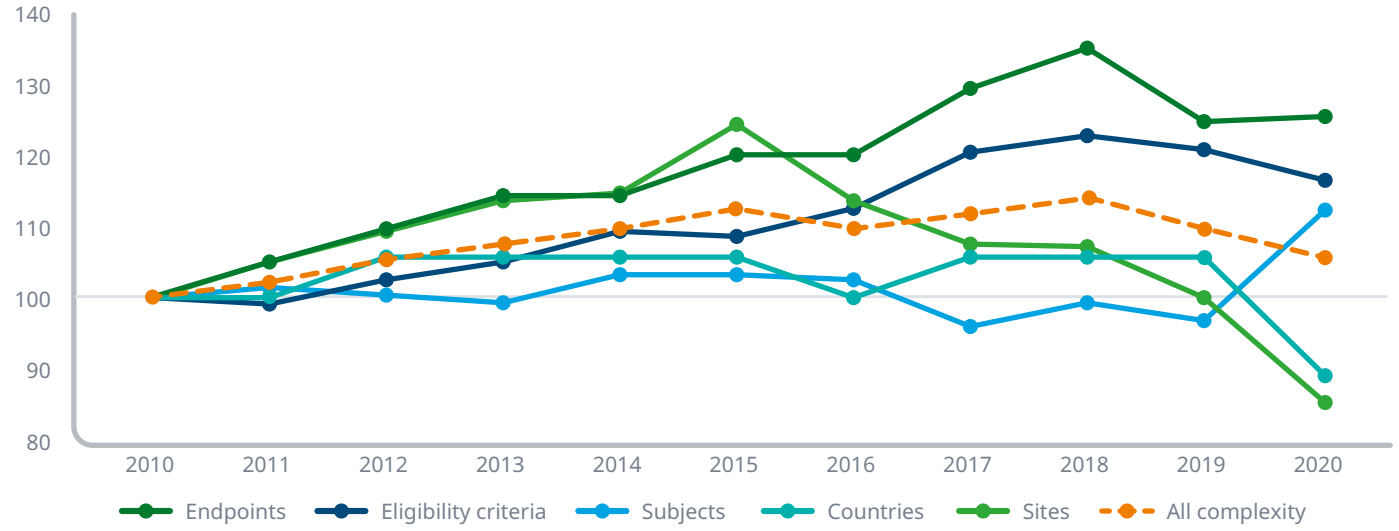
Source: IQVIA Pipeline Intelligence, Mar 2021

- In assessing drug success rates, explicit events such as suspension or discontinuation of a trial are rarer than inferred failures due to inactivity. This is common because companies generally do not announce failures as often as they simply stop making updates, and thus failure without explicit notifications can only be observed after a sustained period of inactivity.
- Inactivity for a period of greater than three years is deemed inactivity, and in 2020 there has been a 15% reduction of active early phase medicines and about 2% for later phases, which results in dramatically higher numbers of newly inactive drugs.
- The nearly 200% increase in these failures in a single year appear to be an anomaly of companies' activities during the COVID-19 pandemic rather than the result of more traditional risks in research.
- While some companies had their trials disrupted, these were most often reported as pauses or delays to the start of recruiting, which would leave the vast majority of trials still active.
- The relatively stable trends in products which proceeded to subsequent phases requires no adjustment in the calculation of success rates.
- Depending on the strategic decisions of sponsors and the duration of disruptions from the pandemic, some if not all of these incremental 'failures' may ultimately be deemed to have been temporary and return to active status, and result in a restatement of composite success rates.

Exhibit Notes: Success is determined as a medicine progressing to a subsequent phase, including approval, and includes those situations where phases are skipped as in an approval of a drug directly from Phase II. Failure includes explicit discontinued, suspended, withdrawn statuses derived from companies or public sources, as well as inferred inactivity due to the absence of any updates for three years. Estimates of the overall reduction in the active research pipeline are based on extrapolations of historic trends compared to observed active records and cannot solely be attributed to the impact of the COVID-19 pandemic.

Clinical trial complexity declined in 2020 predominately from the reduced number of sites and countries, likely related to COVID-19

Exhibit 16: Elements of Complexity Indexed to 2010 Values, All Phases 2010–2020



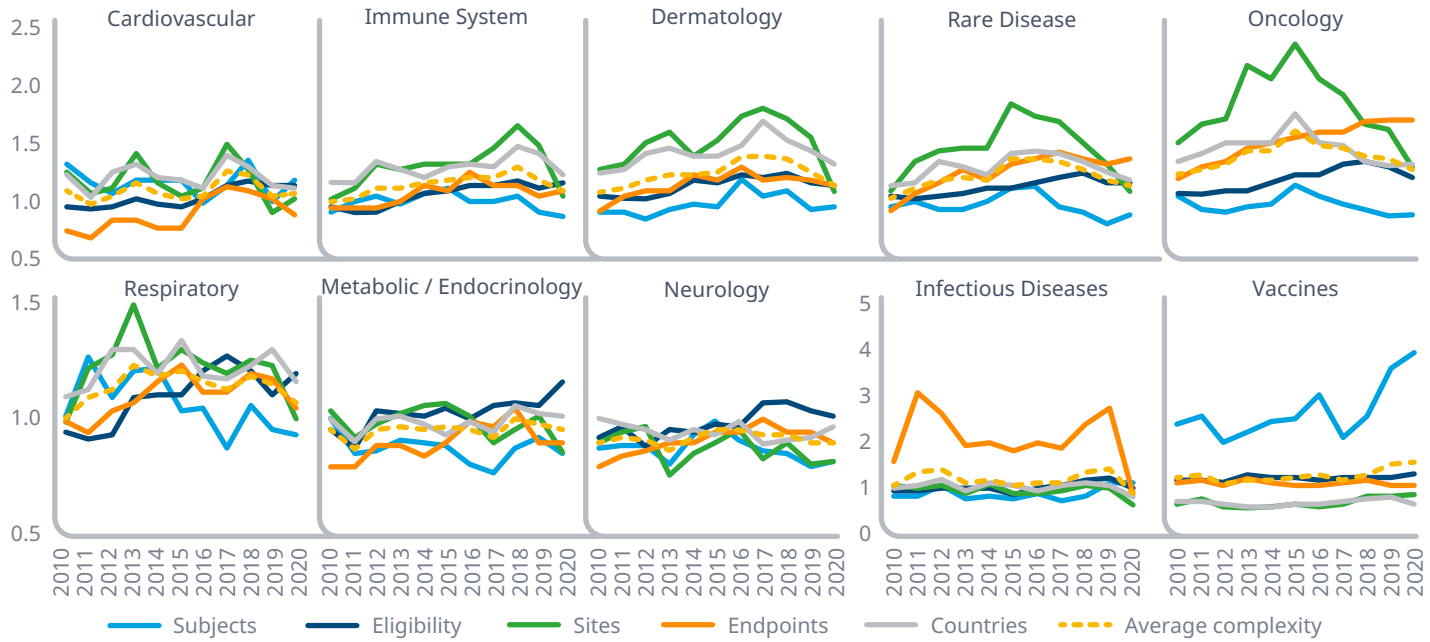
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021; IQVIA Linguamatics, Apr 2021

- Clinical trial complexity has declined in the past two years after generally rising since 2010 and fell in 2020 due to pandemic-related declines in the number of countries and sites which more than offset an increase in the average number of study participants.
- Clinical trial complexity has declined for the last two years from slightly fewer endpoints and eligibility criteria in trials starting in 2019 and 2020.
- In 2020, countries and sites dropped by the largest amount over the past 10 years, likely associated with COVID-19.
- The number of subjects on average also jumped in 2020, also a likely result of the rapidly started COVID-19 trials for vaccines and therapeutics.
- These measures, while not definitive in determining the complexity of operating a trial, do provide a useful guide to the shift in activity required of trial investigators and sponsors and are useful as a guide for the ongoing effort associated with trials.
- Some diseases which are inherently complex to manage, such as those with multiple complications, may not seem to be directly measured by these complexity indices, but very commonly have greater numbers of endpoints and eligibility criteria.

Exhibit Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Infectious diseases excludes vaccines.

Trial complexity factors vary in their relative importance and trajectories over time

Exhibit 17: Trial Complexity by Element and Therapy Area, 2010–2020



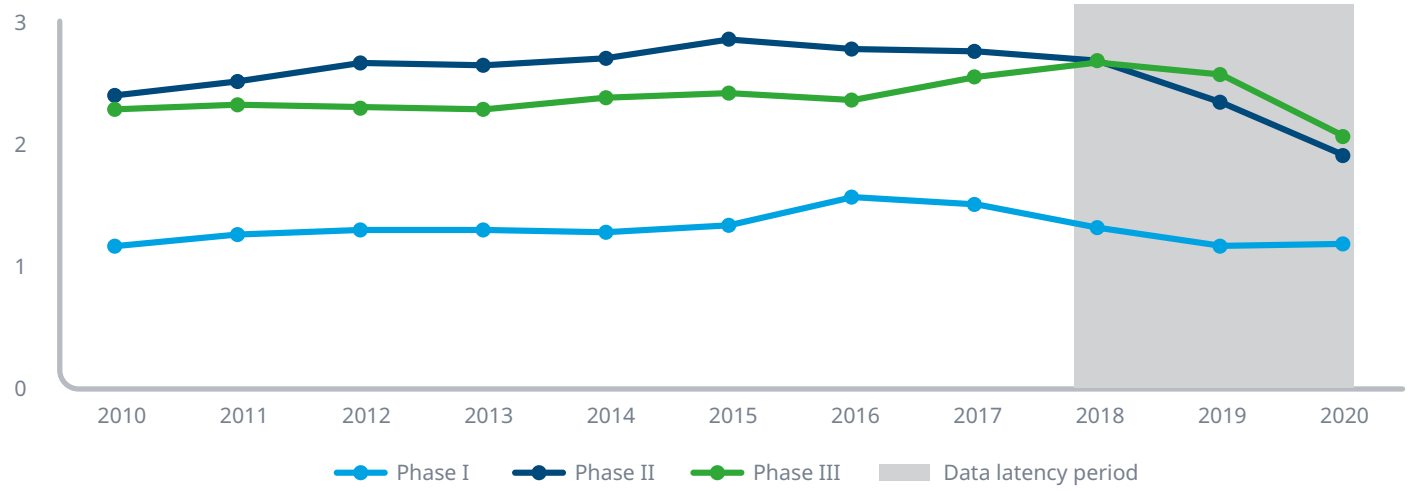
Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021; IQVIA Linguamatics, Apr 2021

- Trial complexity has been rising generally as all of the component indices have seen increases, but at a disease level, only cardiovascular trials and vaccines had higher overall complexity in 2020 than in 2019.
- Complexity overall has dipped in 2020 across most diseases, most commonly from fewer sites and countries as a result of the COVID-19 pandemic.
- Oncology trials are among the most complex using the index, though this has been declining since 2015 as trials have had fewer subjects and sites, likely related to the overlap with rare diseases.
- Rare diseases have seen declining complexity indices since 2015, mostly due to fewer sites, countries and subjects, signaling a focus on even smaller rare disease populations from the approvals we can expect in the next five years.
- Trials in metabolic and endocrinology have an increasing number of eligibility criteria, reflecting how trials must be designed to demonstrate benefit after the failure of existing treatments, driving complexity for new studies.

Exhibit Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Infectious diseases excludes vaccines.

Trial durations are generally understood to be increasing but are skewed by a minority of trials with very rapid completion

Exhibit 18: Average Trial Duration in Years by Phase, All Therapy Areas, 2010–2020



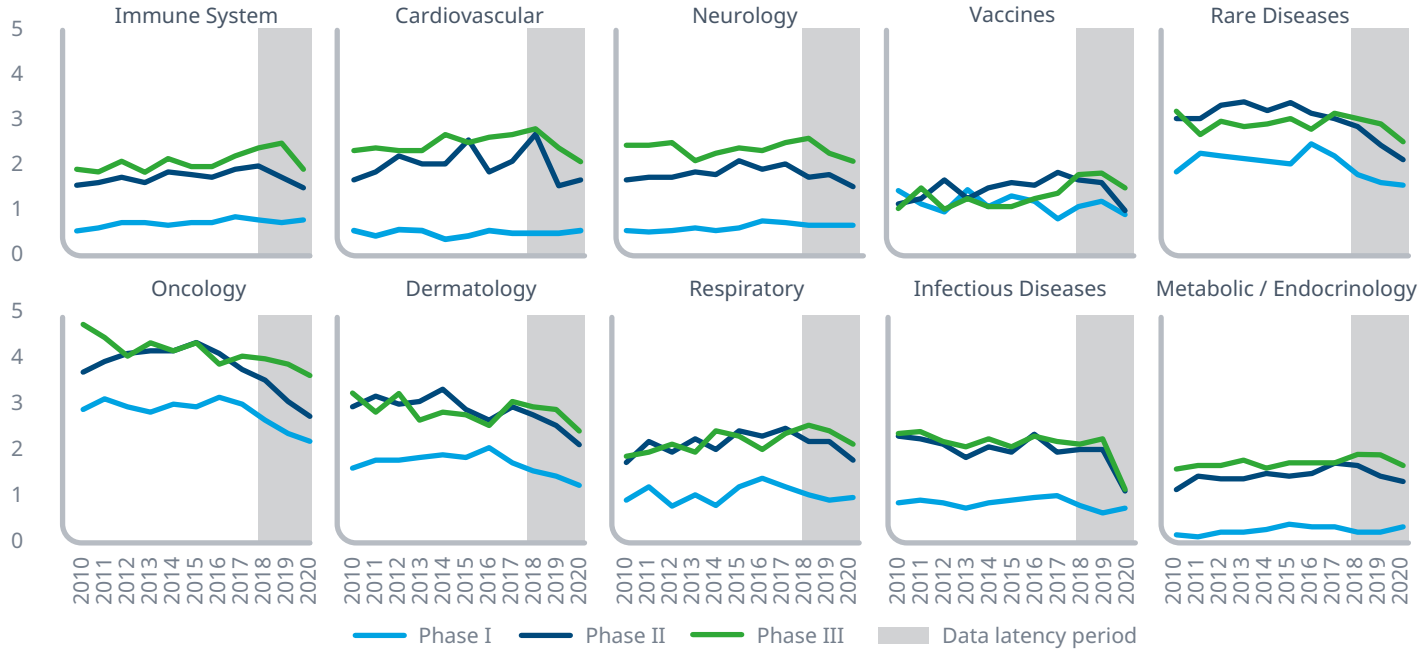
Source: Citeline Trialtrove, Apr 2021

- Trial durations appear to be declining across a wide range of diseases due to a combination of regulatory approval pathways based on faster timeframes, interim results or smaller populations, as well as improvements in operational efficiency.
- These trends may be overstated due to being reported as 'planned completion' and not the actual confirmed dates. Prior to the most recent three years, the majority of trial durations were based on actual completion, whereas the most recent periods have less than 50% of trials with actual dates and include a mix of very accelerated actual trials as well as potentially unrepresentative estimates from sponsors.
- As a contrast, some of the recent trials completed in infectious diseases and vaccines are likely accurate even though they are far below historic averages.
- In 2020 and 2021 there have been some notable shifts in trial durations, focused on respiratory and infectious diseases, suggesting a direct impact from COVID-19 and that at least some of the reductions in duration are related to real events and not data artifacts.
- As a result of these data latency issues, the duration information for 2017 is used for 2018 to 2020 in productivity indices, and these indices may be restated in later updates as actual durations are more reliably reported.

Exhibit Notes: Trial durations are calculated as the time between trail start and the completion of the primary endpoints even as some trial activity may continue after this. In the data latency period, more than 50% of trials report planned end dates, which in combination with actual end dates that are unusually rapid, skew the durations downward in a pattern which is consistently restated over time. For analysis in the development productivity index, the last pre-latency period (2017) is used as the duration for the subsequent years.

Trial duration has been declining for many diseases over the past five years with a pause or reversal in 2020

Exhibit 19: Average Trial Duration (years) by Phase and Therapy Area, 2010–2020



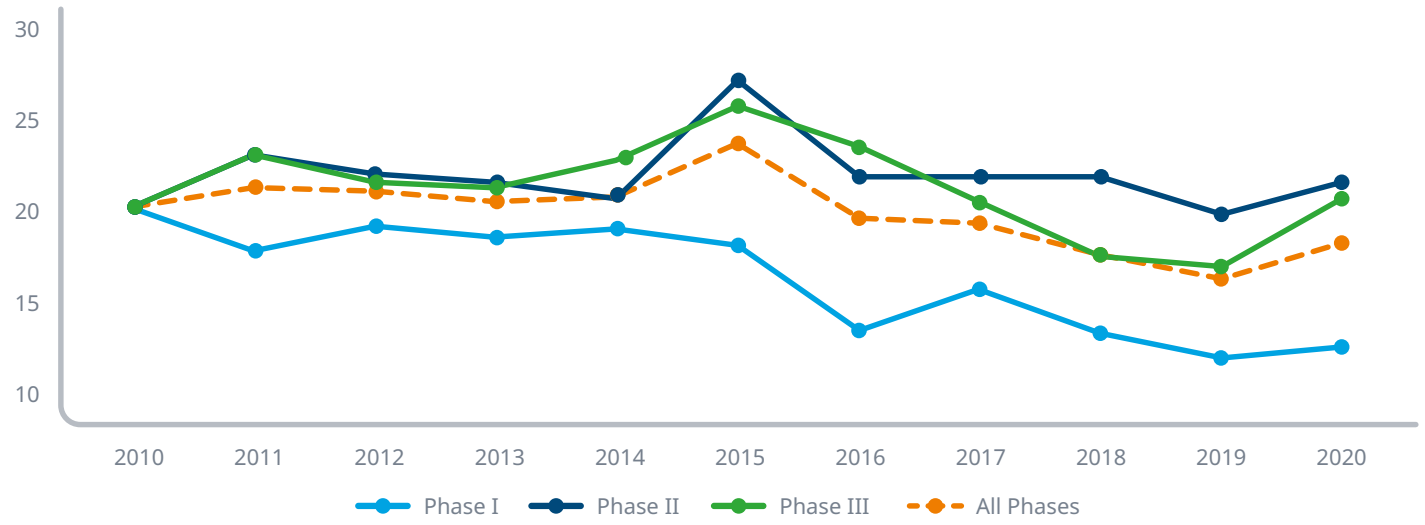
Source: Citeline Trialtrove, Apr 2021

- Across diseases, the greatest variations in trial duration are in Phases II and III, with vaccine Phase II trials averaging 18 months and oncology averaging 3 years and 8 months.
- Phase I trials are often very short, with all but rare diseases, oncology and dermatology averaging less than a year.
- Trial durations are generally stable across diseases, excluding the data latency period of the last three years, but durations could include both downward and upward pressures, some of which are visible prior to 2017.
- Upward pressures in higher population diseases would be the need to observe treatments for a longer period – in cancer, for example – to demonstrate an overall progression-free survival benefit over an existing therapy.
- Downward pressures on trial durations might be a result of diseases with large unmet needs and rare populations being deemed appropriate for smaller populations, though this is often mitigated by the challenges in finding these patients, who in some rare diseases don't know they have the disease for years despite unresolved symptoms in what is often called a diagnosis odyssey.

Exhibit Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Trial duration is based on trial dates reported in clinical trial databases. Trial start date is the date on which the enrollment of participants for a clinical study began. Trial end date corresponds to when the trial ended or is expected to end. Vaccine trials are infectious disease only. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Infectious diseases excludes vaccines.

The composite Clinical Development Productivity Index rose in 2020 after having declined since 2015

Exhibit 20: Clinical Development Productivity by Phase and Overall 2010–2020

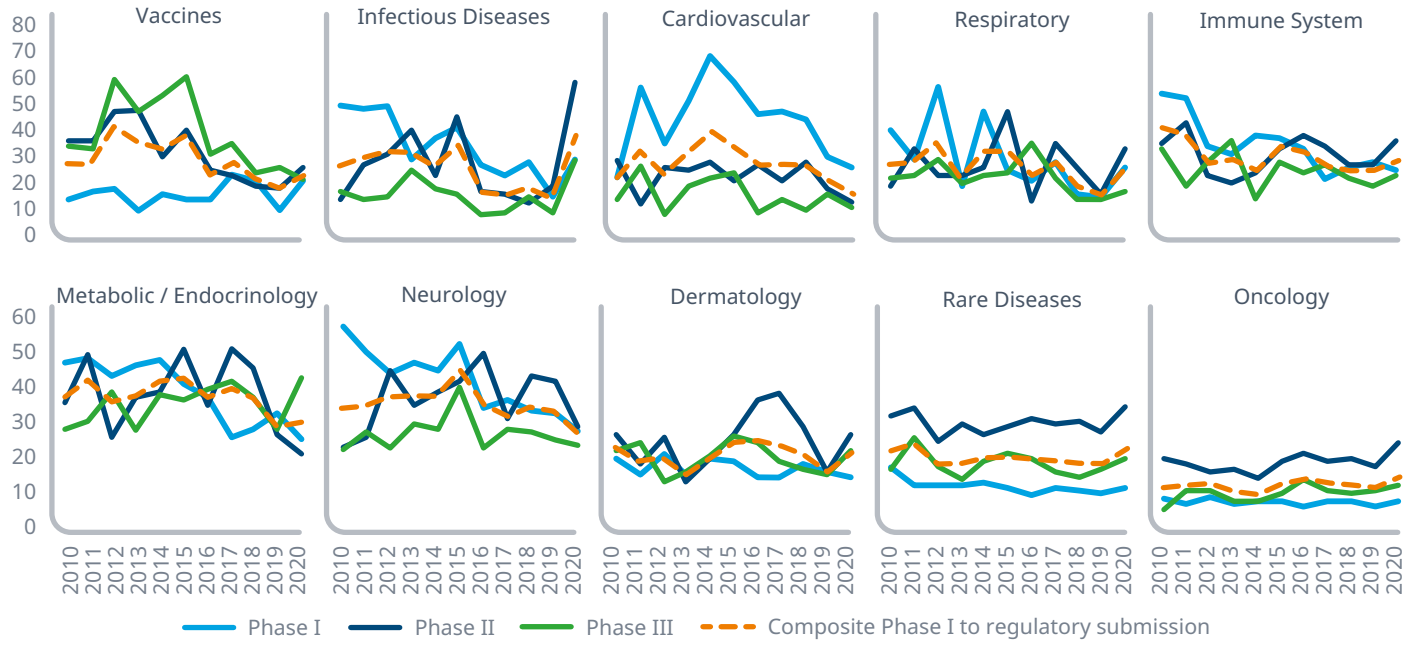


Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021; IQVIA Linguamatics, Apr 2021

- Most diseases have declining in productivity over the past decade, which embeds the challenges of achieving clinical results in well-satisfied traditional disease areas such as cardiovascular and endocrinology, as well as shifts in research priorities to more difficult areas such as oncology and rare diseases.
- The increase in the clinical trial productivity index in 2020 was mostly due to an improvement in Phase III trials, widening the gap with Phase I trials, which score significantly lower with this index.
- Phase II trials have consistently been above the overall index as success rates have been trending up and durations have been trending down, even as complexity has been rising in Phase II as rising numbers of endpoints and eligibility criteria are attributes of these trials.
- Productivity remains below historic levels as success rates are below the long-term average, while complexity attributes of trials are generally rising, as are trial durations in many diseases.

Clinical Development Productivity indices were highest for infectious diseases while oncology extends a decade-long trend as lowest

Exhibit 21: Clinical Development Productivity Across All Phases by Therapy Area, 2010–2020



Source: Citeline Trialtrove, Apr 2021; IQVIA Institute, Apr 2021; IQVIA Linguamatics, Apr 2021

- In 2020 the productivity shift for respiratory, infectious diseases and vaccines was notable and likely related to COVID-19.
- The overall decline in productivity across all diseases reflects both the complexity of the research to improve upon well-established therapies, reflected in declining success rates, rising complexity scores and rising durations.
- While oncology and rare diseases remain two of the largest (and significantly overlapping) disease areas, their clinical trial productivity remain among the lowest.
- Neurology has been one of the larger areas of research in recent years, including a range of rare neuromuscular diseases as well as long-hoped-for advances in Alzheimer's, Parkinson's and a range of other diseases, and has notably higher productivity than other areas with more activity and indicates a bolus of neurology output from R&D can be expected in coming years.

Exhibit Notes: CAGR = Compound annual growth rate. Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Data shown is a weighted average. Vaccine trials restricted to infectious disease vaccines only.

R&D pipeline

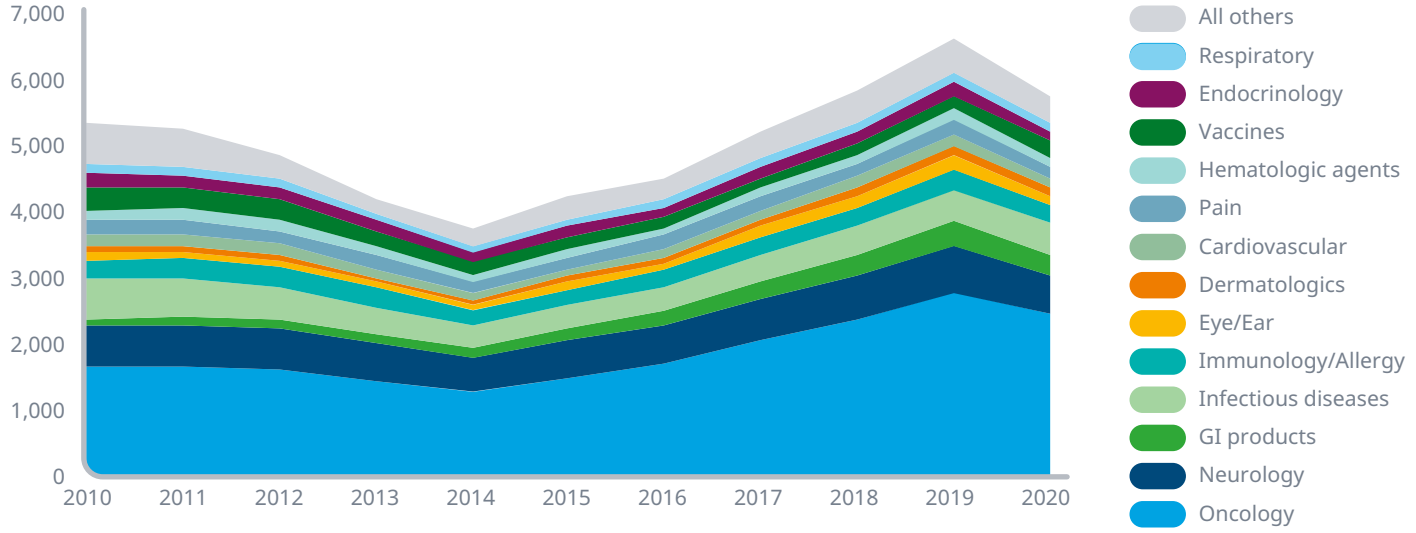
Growth in the early-stage pipeline – including next-generation biotherapeutics – paused in 2020, while the late-stage pipeline grew modestly. In both parts of the pipeline, oncology drugs reached record high numbers and shares of the total pipeline.

- Total early-stage pipeline products declined by 13% in 2020, the first reduction since 2014, bringing the number of total products back to 2018 levels.
- In the late-stage pipeline, the number of products increased by 3%, bringing total expansion of the pipeline to 43% since 2015.
- Oncology drugs represent more than 40% of the early-stage and more than 30% of the late-stage pipeline; both are all-time high proportions of the industry's drug development pipeline.
- Half of the late phase oncology pipeline is for rare cancers and includes a wide range of next-generation and targeted therapies.
- Growth in the pipeline of next-generation biotherapeutics stalled in 2020 after almost doubling in the prior two years, but further growth may be expected as the impact of the pandemic recedes and development programs progress.
- The next-generation biotherapeutic pipeline continues to focus on gene editing, CAR-T and RNA therapeutics in both early and late phases of development.
- Neurology research is significantly focused on Alzheimer's and Parkinson's, with a range of other often rare diseases.
- HIV developments over three-and-a-half decades have contributed to a range of advances in our understanding of immunology, and techniques used in successful (and failed) HIV treatments have likely contributed to the speed of COVID vaccine development.

Growth in the pipeline of next-generation biotherapeutics stalled in 2020 after almost doubling in the prior two years, but further growth may be expected as the impact of the pandemic recedes.

Growth in the early-stage pipeline paused in 2020 and brought the total number of products back to 2018 levels

Exhibit 22: Number of Early-Stage Pipeline Products by Therapeutic Drug Class, 2010–2020



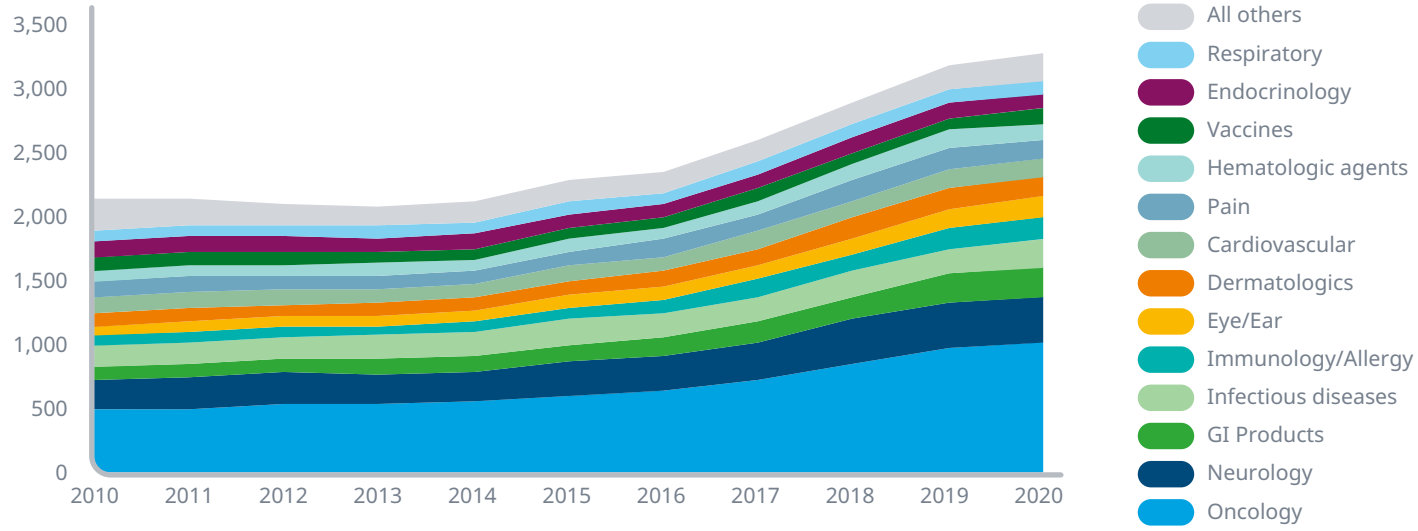
Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- The early-stage pipeline experienced its first attrition since 2014, declining from 6,607 products in 2019 to 5,734 products in 2020.
- The decline is in part due to the pandemic, as emerging biopharma, small, and some mid-size companies needed to pause or terminate their clinical trial activity due to lockdowns, lack of patient availability, and financial constraints.
- Additionally, clinical trial activity that was met with barriers prior to the pandemic was expected to resume in 2020; however, that activity has remained dormant as the financial and logistical constraints presented by the pandemic have not resolved for all companies.
- Oncology remains the focus of the early-stage pipeline, comprising 43% of the pipeline, or 2,455 products.
- Similar to the late-stage pipeline, neurology comprises 10% of the early-stage pipeline, or 573 products.
- The therapy area with the highest CAGR since 2015 is GI products (14%), which is mostly focused on rare diseases.
- Oncology has the second-highest CAGR since 2015 (11%), followed by eye and ear treatments (9%), which have seen advances in gene and cell therapies.

Exhibit Notes: Does not include products in the pipeline that have an undisclosed high class therapy, which includes 55,851 products from 2010-2020.

Growth in the late-stage pipeline continued in 2020, bringing total expansion to 43% since 2015

Exhibit 23: Number of Late-Stage Pipeline Products by Therapeutic Drug Class, 2010–2020

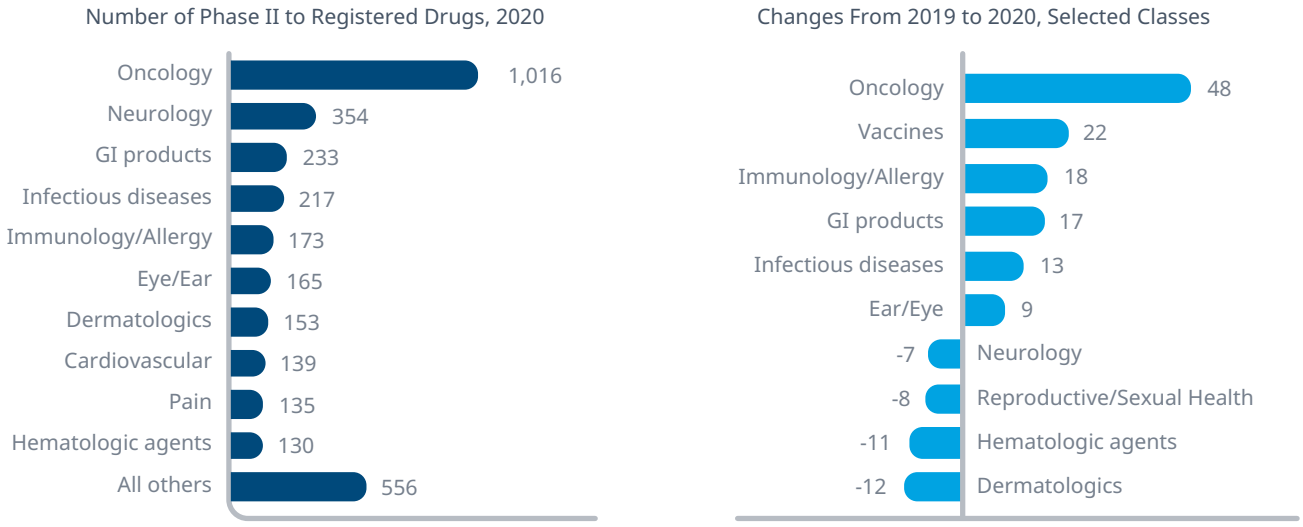


Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- The late-stage pipeline expanded by 43% during the past five years and portends sustained levels of new drug approvals and launches over the next five years.
- There are currently 3,271 products in development in the late-stage pipeline, with 1,016 in development in oncology.
- The next highest portion of the pipeline, neurology, comprises 11%, or 354 products in 2020. The remaining therapy areas each comprise 7% or less of the late-stage pipeline.
- Over the past 10 years, oncology has grown from comprising 23% of the pipeline in 2010 to 31% in 2020. All other therapy areas have comprised a similar share of the late-stage pipeline over the past 10 years.
- Since 2010, the fastest growing therapy areas in the late-stage pipeline have been eye and ear treatments and GI products (9.4% CAGR from 2010–2020, each), following by immunology treatments (8.2%).
- While oncology has comprised the largest portion of the pipeline, its CAGR from 2010–2020 is the third highest at 7.5%.

Oncology drugs represent more than 30% of the late-stage pipeline, and this class continues to grow the most

Exhibit 24: Late-Stage Pipeline Products in 2020 and Changes from 2019 in Selected Classes

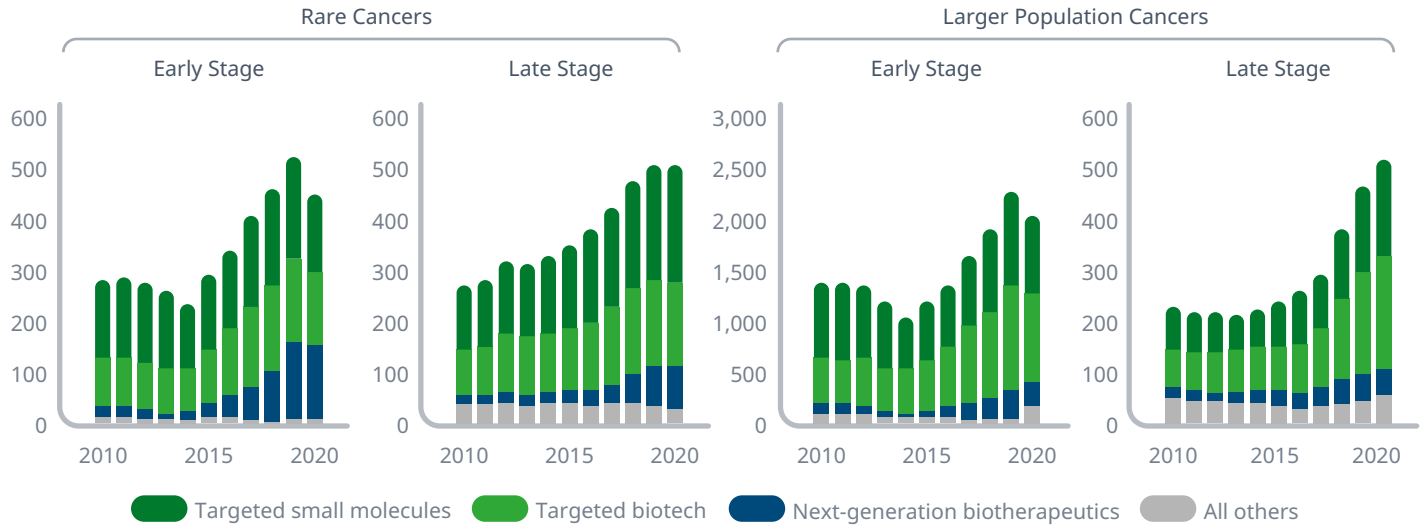


Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- In 2020, products were added to the late-stage pipeline in key disease areas, including oncology, neurology, and gastrointestinal products.
- Oncology now has 1,016 late-stage products, up 48 products since 2019, an increase of 5%.
- Perhaps unsurprisingly, vaccine products increased by 22% as companies sought to quickly respond to and stem the COVID-19 pandemic worldwide.
- Immunology and allergy treatments increased by nearly 12%, or 18 products, now numbering 173 products in total.
- There were some reductions in late-stage pipelines, including neurology and dermatology. Neurology decreased by 7 products, while dermatology decreased by 12 products.

Half of the late phase oncology pipeline is for rare cancers and includes a wide range of next-generation and targeted therapies

Exhibit 25: Number of Early-Stage and Late-Stage Oncology Pipeline Products by Type, 2010–2020



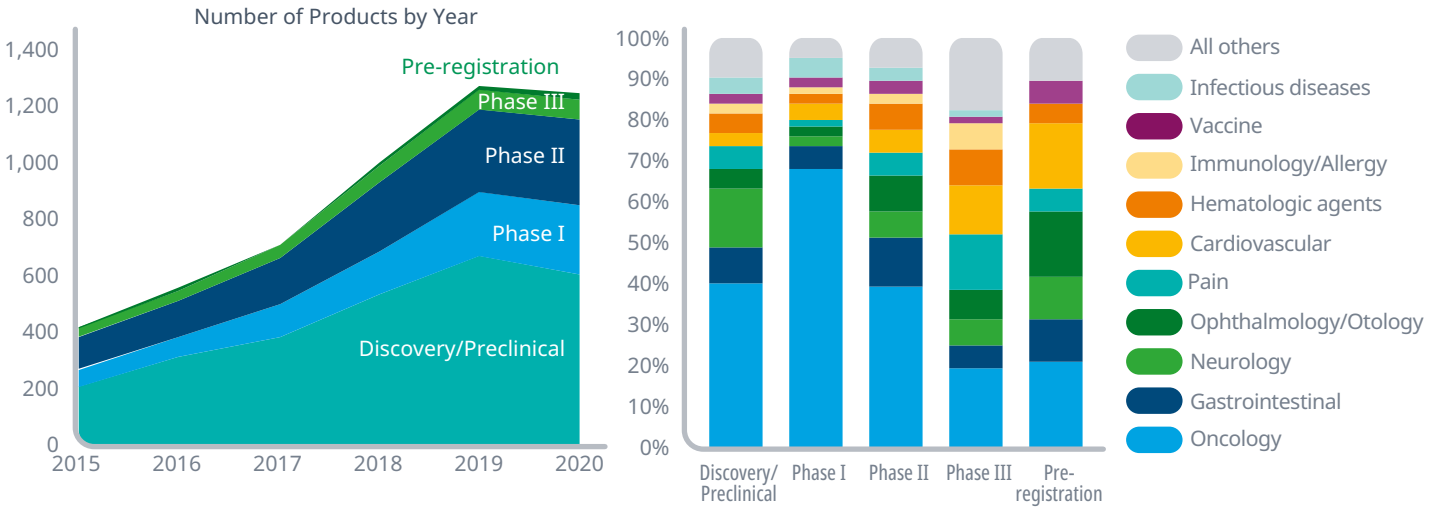
Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- In 2020, about 500 products were in late-stage development for rare cancers, similar to the number in late-stage development for larger population cancers.
- Rare cancers also have a relatively similar number of products in development in both early and late phases, reflecting the continued flow of rare disease treatments that can be expected in the future.
- Rare cancers in early phase may be understated as earlier phase research often cannot determine specific rare tumor applicability when only general solid tumor or leukemia or lymphoma cancer types are suspected by researchers at the time.
- With rare oncology drugs having a composite success rate of 33%, many of these early-stage medicines can be expected to reach later phases and ultimately the market, often with accelerated timelines.
- Targeted small molecules and biologics include many of the newest immuno-oncology treatments, checkpoint inhibitors, kinase inhibitors, and treatments linked to dozens of biomarkers, which are notable for allowing clearer demonstration of efficacy in trials.
- Oncology research has a small but important focus in next-generation biotherapeutics, which include a range of cell and gene therapies, gene editing, and RNAi therapies, which promise significant precision and efficacy even as only a few such treatments have reached the market to-date.
- As many of these targeted or next generation treatments relate to genetic mutations or predispositions, the rising use of genetic sequencing is enabling a growing pool of knowledge about both diagnosed and undiagnosed patients.

Exhibit Notes: Analysis includes medicines in active research with a focus on cancer therapeutics and does not include supportive care. Medicines are considered targeted if their mechanism of action uses a specific biomarker to target treatment within the body. Many cancer drugs have multiple tumors in research, and drugs which have any trials focused on rare cancers have been included as rare. Drugs which have no rare tumor targets are considered larger population. All other includes a range of cytotoxic, hormonal and radiotherapeutic mechanisms without a targeting mechanism.

Growth in the pipeline of next-generation biotherapeutics paused in 2020 after almost doubling in the prior two years

Exhibit 26: Next-Generation Biotherapeutic Products Pipeline by Phase and Therapeutic Drug Class

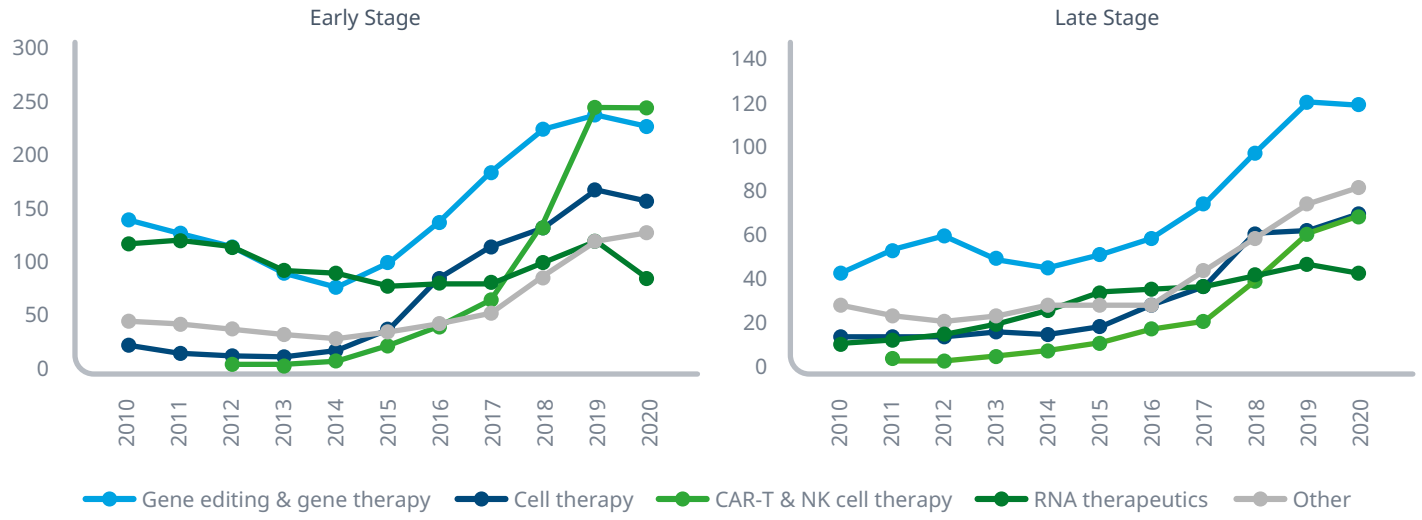


Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- There are 1,243 products throughout the next-generation biotherapeutics pipeline, with nearly half of them (606) in the discovery/preclinical development phase.
- Similar to the overall pipeline, there was slight attrition in 2020, in part due to the COVID-19 pandemic affecting clinical trial feasibility and realized financial constraints.
- Phase II is currently a robust portion of the pipeline, indicating earlier success rates are potentially increasing as these technologies come into themselves.
- Late-phase represents a very small portion of the pipeline, reflective of the difficulty of reaching this stage. It also underscores how the regulatory journey of these products may differ, as Phase II clinical data may be sufficient for FDA approval.
- Next-generation biotherapeutic development remains focused in oncology overall but is now entering other disease areas that affect larger swaths of the population, including cardiovascular diseases, pain, and neurological disorders.

The next-generation biotherapeutic pipeline is focused on gene editing, CAR-T and RNA therapeutics in both early and late phases

Exhibit 27: Next-Generation Biotherapeutics Early- and Late-Stage Pipeline by Mechanism



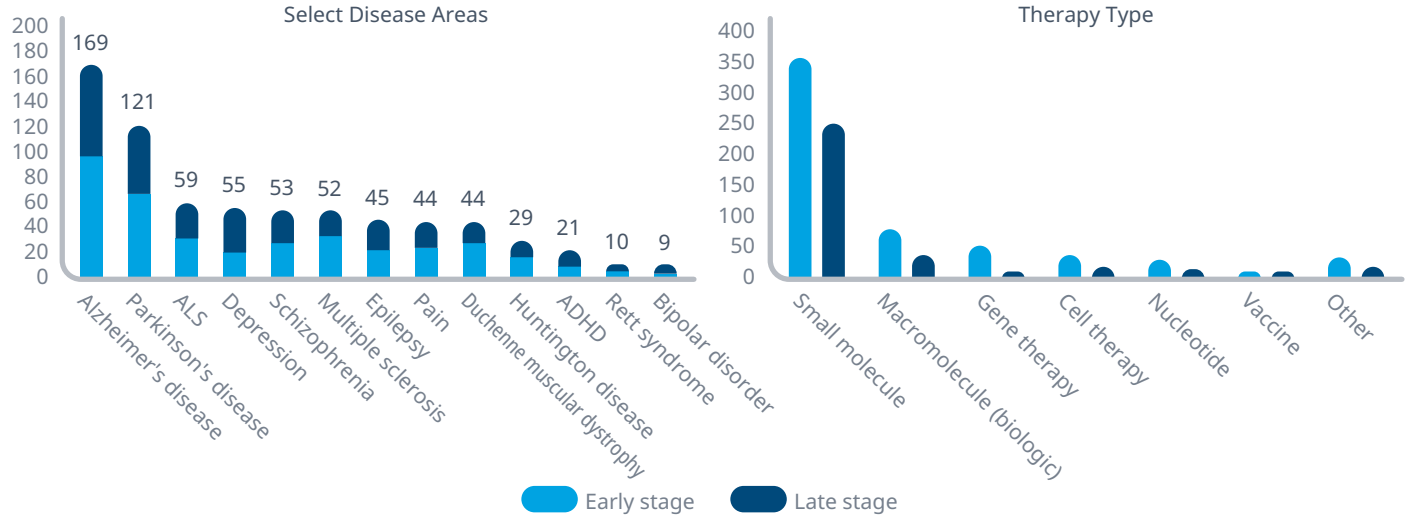
Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- The complete sequencing of the human genome in 2000 has fundamentally changed how disease and treatment are thought about. As a result, many gene therapies were developed in the early 2000s.
- As the difficulties of gene therapy became apparent, including proper gene targeting and delivery, patient availability, manufacturing, and failure of many therapies, the gene therapy pipeline reduced in the early 2010s.
- As gene therapies were waning, the RNA-based therapeutic pipeline began increasing as an alternate way of gene expression modification became possible.
- In the past 10 years, there has been a resurgence of gene therapies, now including gene editing technologies such as CRISPR, and chimeric antigen receptor T (CAR-T) cell therapies.
- Gene therapies are targeting rare diseases, including gastrointestinal diseases such as lysosomal storage disorders, as well as congenital blindness and cancer.
- Gene and cell therapies for diseases such as diabetes are now entering the clinic, suggesting these technologies will offer viable treatment options for large patient populations.
- RNA-based therapeutics, including RNA interference (RNAi) – the inhibition of expression of certain genes by mRNA – are also focused on rare gastrointestinal diseases and oncology, and more recently have moved to cardiovascular diseases.

Exhibit Notes: Active trials only.

Neurology research is significantly focused on Alzheimer's and Parkinson's with a range of other often rare diseases

Exhibit 28: Number of Products in Neurology Pipeline in 2020 by Disease, Therapy Type and Stage



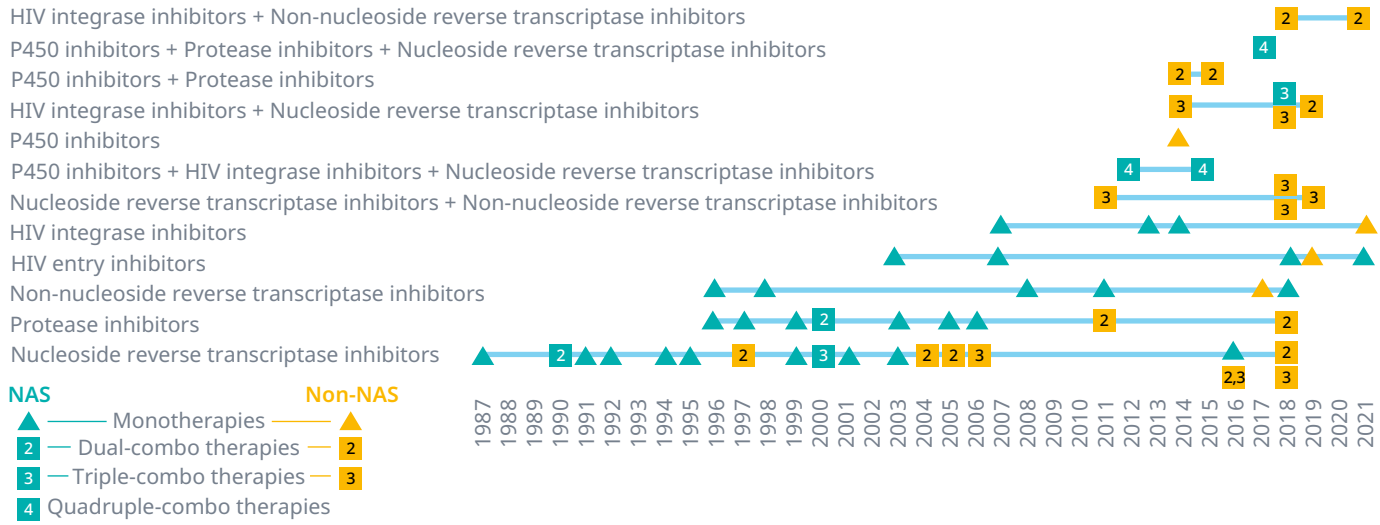
Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- There are currently 354 products under investigation in the neurology pipeline, including products to treat the nervous system, mental health, and pain.
- There is a significant focus on Alzheimer's and Parkinson's diseases, which account for 169 and 121 products, respectively.
- Other devastating diseases, such as ALS and multiple sclerosis, continue to show promising pipelines, with a majority share in early-stage development.
- Currently, 62% of the early-stage pipeline and 74% of the late-stage pipeline is comprised of small molecule products, indicating their continued utility in a rapidly evolving space.
- Next-generation biotherapeutics, such cell and gene therapies, each comprise less than 10% of the early-and late-stage pipelines but could be the most promising technologies.
- Unmet needs in Alzheimer's and Parkinson's, in particular, if addressed with new therapies, could be significant, especially considering the historically low numbers of new medicines in those diseases.

Exhibit Notes: Therapy type segments are non-overlapping and macromolecules (biologics) are those biologic products that are not otherwise noted.

HIV research continues to produce new highly effective and tolerable treatments for managing HIV and preventing spread

Exhibit 29: HIV New Medicines by Mechanism and Type of Product 1987 to April 2021



- Small molecule therapies have been developed over the past three decades, including many with strong efficacy, which has made living with HIV a chronic disease.
- Most HIV patients have taken a complex regimen of multiple drugs throughout the day, generating a significant 'pill burden,' whereas newer therapies are increasingly combination products with greater efficacy and tolerability as well as once-a-day convenience, contributing to stronger adherence and therefore, better outcomes.
- Meanwhile, decades of investment in vaccines has failed to produce a success, and with HIV endemic in many areas of the world, having effective treatments does not mean there is not a need for a vaccine for HIV.
- The failure of vaccines, though unfortunate, has driven research focus and paved the way for understanding complex viral etiologies. As the COVID-19 pandemic hit, the many pitfalls in immunology and vaccines research identified by past HIV failures have allowed the successful development of novel vaccines in record time.

Exhibit Notes: HIV Therapies have been displayed based on the mechanisms of action present in the medicines of either single-ingredient or fixed-dose combination therapies. The number of ingredients in the combinations are indicated with the numbers 2, 3 or 4. New active substances (NAS) are defined as a drug or fixed-dose combination where at least one ingredient is entirely new. Non-NAS include combinations of previously launched ingredients, or reformulations or delivery system changes.

R&D funding

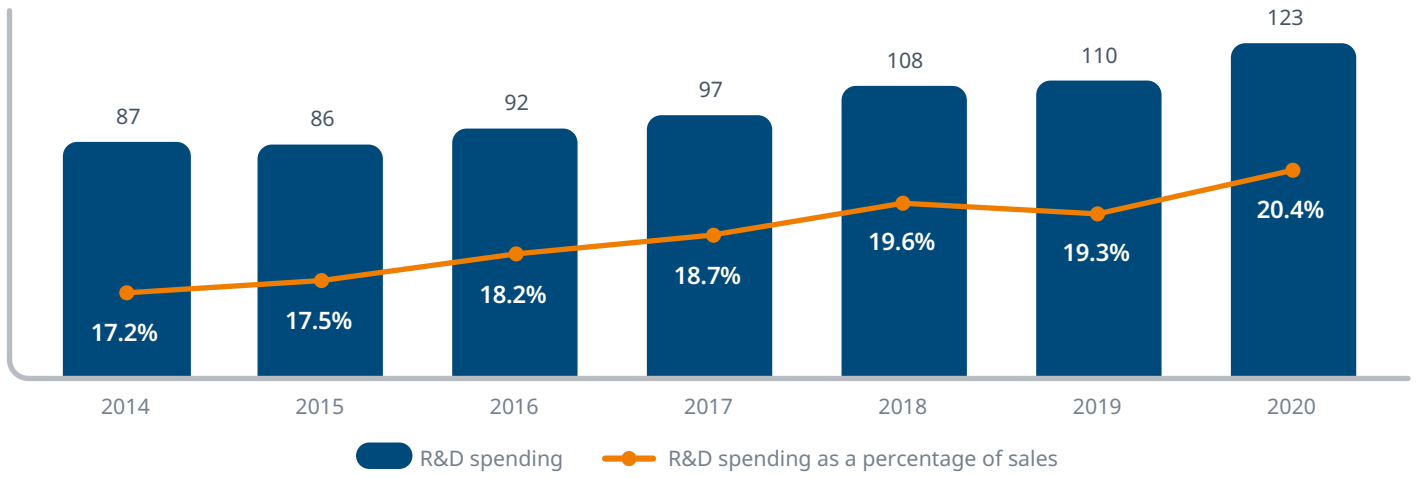
Funding for early and late-stage R&D increased significantly in 2020, unaffected by the disruptions of COVID-19 and reflecting a strong focus on innovative pathways and approaches to discover and develop novel therapeutics. Strategic transactions – ranging from M&A through licensing and other forms of collaboration, often between large and small companies – also proceeded at typical levels, buoyed by a significant amount of interest in COVID-19-related deals.

- Aggregate R&D expenditures by the 15 companies with the highest pharmaceutical sales reached $123 billion in 2020 and exceeded 20% of sales for the first time, increasing 43% over the prior five years (since 2015) while sales for these companies increased by 23% over the same period, reflecting the strong commitment by these companies to growth through innovation and R&D investment.
- Venture capital flows into the life sciences rose by 50% in 2020 over 2019 levels as interest and valuations in early-stage companies remained at all-time highs despite the pandemic.
- Strategic transactions – including M&A, licensing and collaboration deals – were buoyed by COVID-19 deals, including ones related to the launch of vaccines developed in under a year during the pandemic.
- COVID-19 related deals were much more commonly partnerships or supply agreements than outright mergers as companies attempted to ramp up quickly to face the pandemic, while the character of non-COVID-19 deals changed as well due to the lack of face-to-face meetings and the caution of some companies in the light of strategic uncertainty.
- Oncology remains the largest area of deal-activity, consistent with its share of the overall pipeline.
- Emerging biopharma companies are responsible for most of the late-stage pipeline, though their share fell in 2020.
- Drugs from China-headquartered companies have risen to 12% of the early-stage pipeline from 2% a decade ago, even as European companies have seen their share drop from 33% to 22%.

Aggregate R&D expenditures by the 15 companies with the highest pharmaceutical sales reached $123 billion in 2020 and exceeded 20% of sales for the first time.

R&D expenditure by large pharma corporations totaled a record $123 billion in 2020, and exceeded 20% of revenue for the first time

Exhibit 30: Large Pharma R&D Spending and Spending as a Percentage of Sales 2016–2020, US$Bn



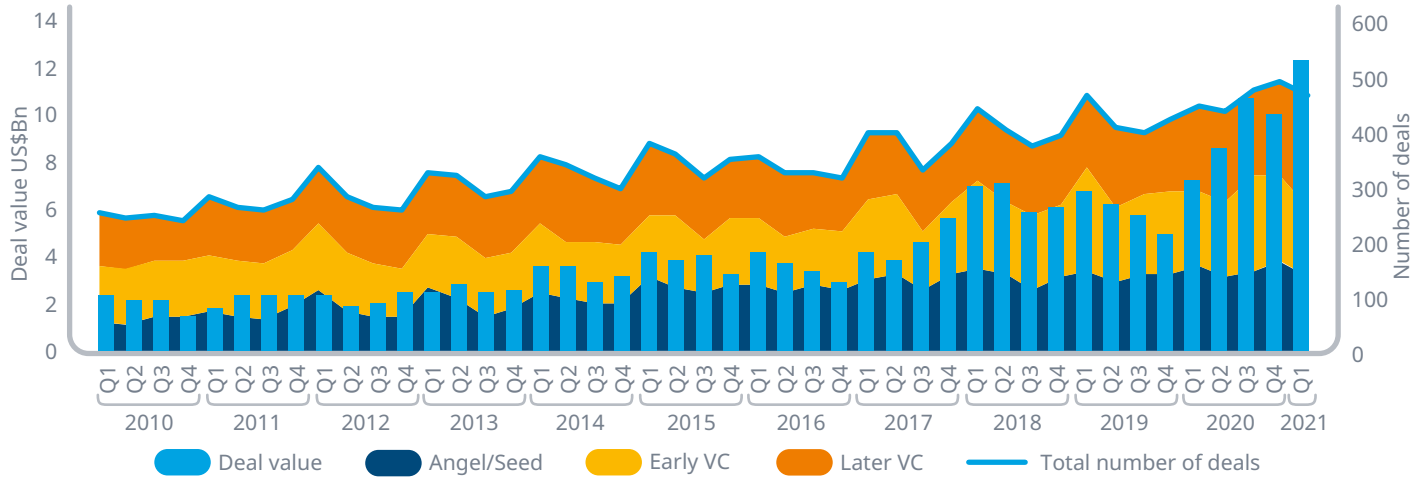
Source: Data taken from company financial statements; IQVIA Institute, Feb 2021

- The largest pharmaceutical companies together spent more than $123 billion on research and development in 2020, up 12% from 2019.
- The total includes the impact of acquisitions, e.g., the Bristol Myers Squibb acquisition of Celgene.
- Across these companies, R&D exceeded 20% of revenue in 2020 for the first time.
- Since 2015, R&D spending for large companies has increased by 43.6% with a five-year CAGR of 7.5%.
- R&D expenses can include write-offs of failed R&D programs developed internally or acquired, which can bring year-to-year variability in the level of total spending.
- These represent the total company view, and some divisions such as consumer health are typically less R&D-intensive than the pharmaceutical division.

Exhibit 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.

Venture capital deal activity and investment flows accelerated in 2020 as interest in life sciences intensified

Exhibit 31: U.S. Life Science Venture Capital Deal Value in US$Bn and Number of Deals Closed by Type



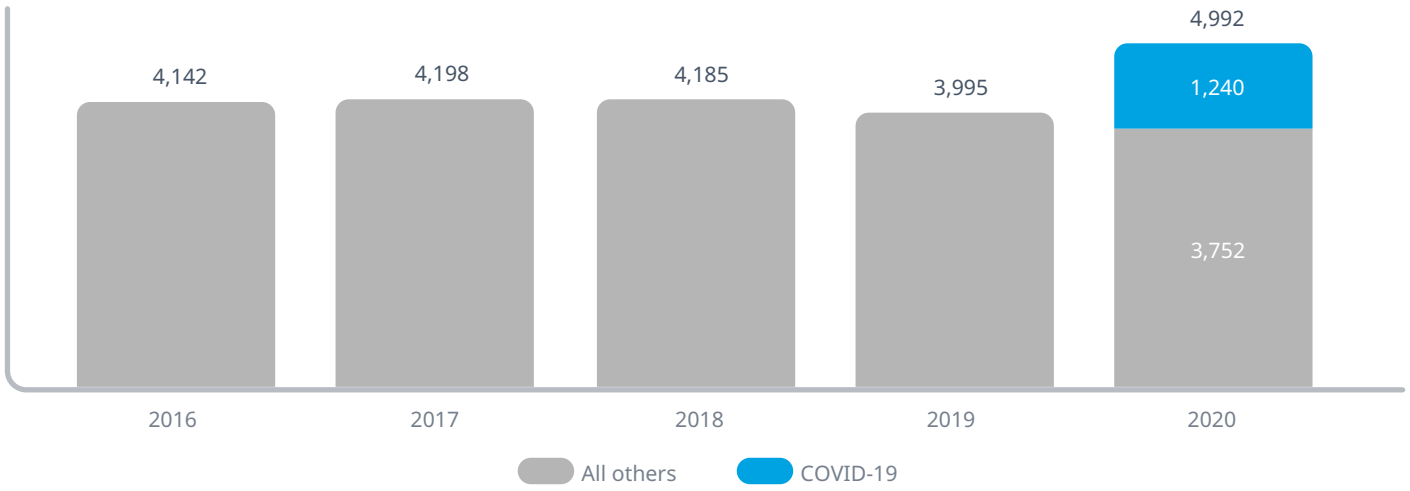
Source: Q1 2021 PitchBook-NVCA Venture Monitor, accessed Apr 2021. Available from: https://pitchbook.com/news/reports/q1-2021-pitchbook-nvca-venture-monitor

- Life sciences venture capital deals continue to grow, with an uptick in investment in later-stage deals.
- There was a peak number of deals – 1,738 in 2020, 12% higher than 2019, but slowing to 4.7% in the first quarter of 2021.
- Deal value jumped up 57% between 2019 and 2020, reaching $34.9 billion, driven by the increased proportion of later venture capital deals, which typically draw more dollars. This corresponds to an 18% CAGR since 2015.
- The escalation of deal value in 2020 and into 2021 represents a significant shift in trajectory and reverses a flat-to-declining trajectory in 2018 and 2019.
- The number of angel and seed deals continues to grow, while the number of early venture capital deals has remained more constant since 2017.

Exhibit Notes: VC = Venture Capital.

Strategic transactions — including M&A, licensing and collaboration deals — were buoyed by COVID-19-related deals

Exhibit 32: Number of Deals by Year

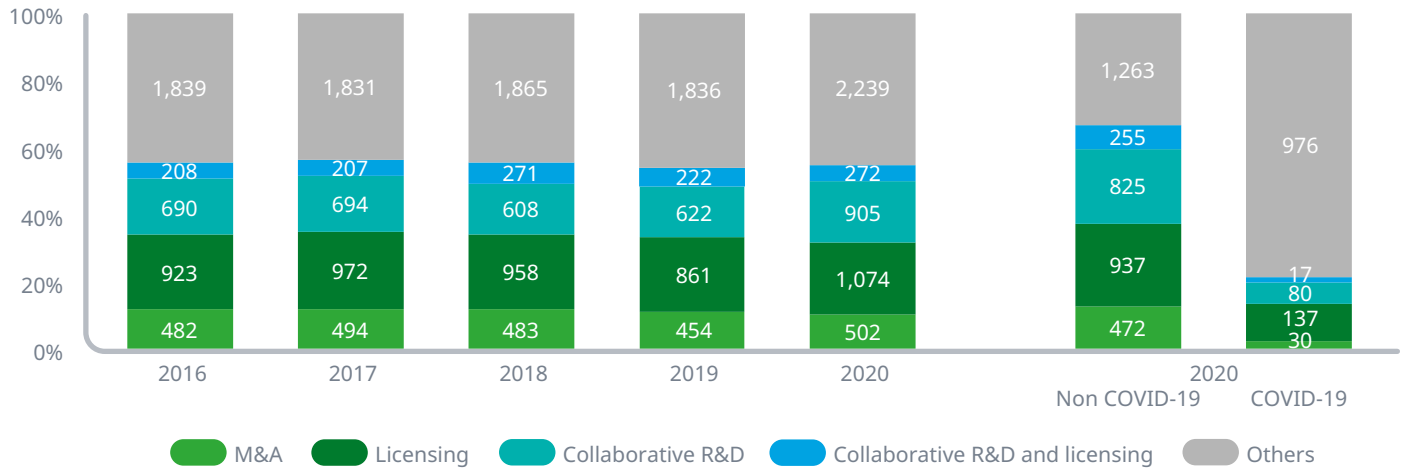


Source: IQVIA Pharmadeals Review of 2020 accessed at: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals-review-of-2020

- Publicly disclosed deal activity reveals that the number of agreements signed, excluding standalone research grants, increased by approximately 25% from 2019 to 2020 in an unmatched annual rise driven by COVID-19, as non-COVID-19 deals fell 6% from 2019 to 2020.
- The M&A process was hindered by a lack of face-to-face contact, particularly for larger deals. Delays to clinical trial enrollments and data read-outs also had an impact on M&A decision-making, while surging asset prices deterred some companies but forced others to move quickly and pay a premium price, or risk losing out on a coveted target entirely.
- The COVID-19 pandemic created multiple licensing and collaboration opportunities for companies with vaccine technologies, diagnostic platforms and antiviral programs. With licensing and collaborative research agreements viewed by some risk-averse companies as a sensible alternative to M&A in a time of great uncertainty, the level of licensing and collaboration activity in the life sciences sector increased significantly.
- Furthermore, disciplined dealmakers increasingly opted for alternative deal structures to M&A, typically broad pipeline-accessing deals with equity components such as Gilead Sciences' 10-year partnership with Arcus Biosciences to co-develop and co-commercialize all current and future therapeutic product candidates in Arcus' pipeline in exchange for $375 M upfront in cash and equity (Deal no. 98195).

Licensing and collaboration deals rose dramatically in 2020 driven by COVID-19

Exhibit 33: Number of Deals by Year and Type, 2016–2020

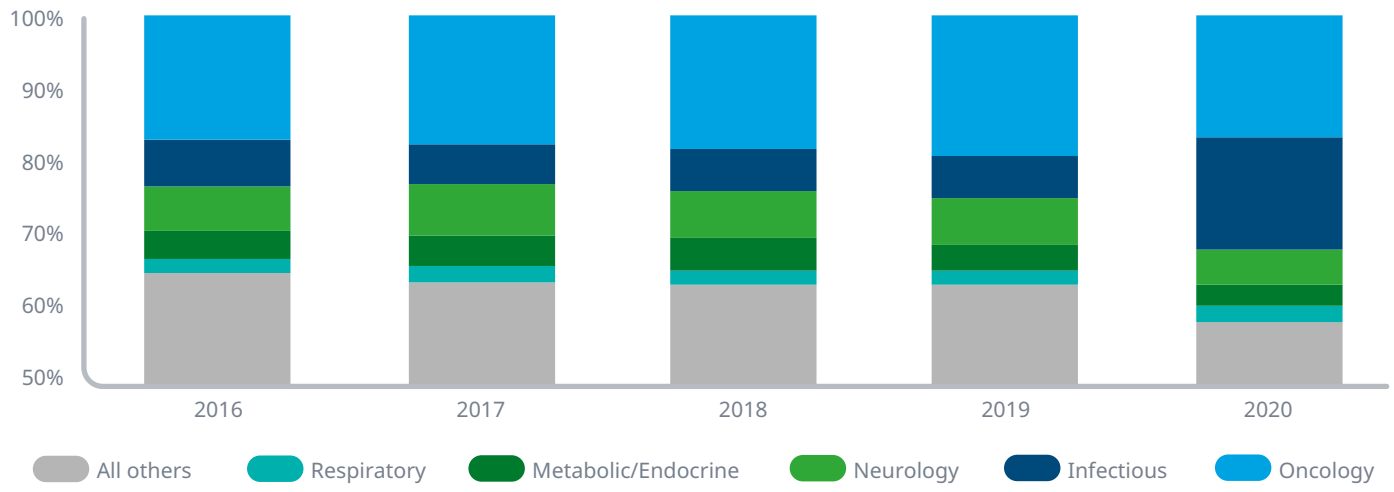


Source: IQVIA Pharmadeals Review of 2020 accessed at: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals-review-of-2020

- Despite the myriad operational challenges presented by the COVID-19 pandemic, the volume of life sciences M&A deals (defined here as Mergers, Business Acquisitions and Divestments, signed but not necessarily completed) announced in 2020 rose 10% from 2019 to 2020.
- These were led by the $39 billion acquisition of Alexion by AstraZeneca to bolster their immunology portfolio.
- Licensing deal volume reached a five-year low in 2019 owing to increasing discernment on the part of licensees, escalating asset valuations, and the ready availability of capital for early-stage biopharmaceutical companies. Many of these factors continued to influence licensing activity in 2020, which was also affected by operational disruption brought about by the COVID-19 pandemic, pipeline prioritization and a desire to preserve cash.
- Life sciences companies rushed to form R&D alliances in H1 2020 to expedite the development of COVID-19 vaccines and therapeutic interventions with the aim of preventing disease or speeding recovery, often broadening the scope of existing collaborations to include COVID-19 R&D.
- Much collaborative activity was also directed toward developing diagnostics to detect past or current infections accurately. As a result, the level of disclosed collaborative R&D deal-making (defined here as discovery or preclinical-stage deals that involve two or more parties actively collaborating on R&D) jumped by an unprecedented 30% from 2019 to 2020 after several years of decline (Figure 13).
- Almost 30% of the collaborative R&D deals signed in 2020 concerned COVID-19; if these are removed from the 2020 data set, then collaborative R&D activity for all other disease areas declined 8% from 2019 to 2020.

Oncology accounts for the most deals, while in 2020 the COVID-19 pandemic has dramatically increased infectious diseases activity

Exhibit 34: Share of Deals by Therapy Area

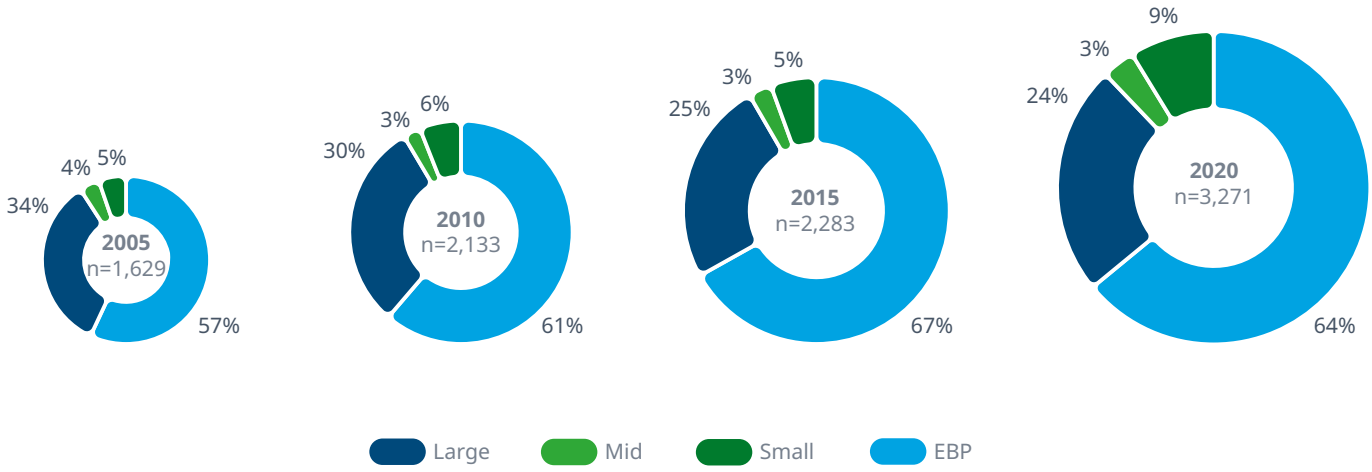


Source: IQVIA Pharmadeals Review of 2020 accessed at: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals-review-of-2020

- Oncology continues to lead the therapy area focus for deals, with 16% of all deals in 2020, down from 19% in 2019.
- These mergers included the Gilead Sciences $21 billion acquisition of Immunomedics with a cancer focus including sacituzumab govetican (Trodelvy) for triple-negative breast cancer as well as their $4.9 billion acquisition of Forty Seven with magrolimab, an investigational anti-CD-47 monoclonal antibody in multiple clinical studies for diseases including myelodysplastic syndrome, acute myeloid leukemia and diffuse large B-cell lymphoma.
- Infectious diseases represented 15% of deals in 2020, up from 6% in 2019 and driven by the swarm of activity in COVID-19.
- Early in the COVID-19 pandemic, many large collaborations were announced for vaccine development including, Pfizer/BioNTech, and Sanofi/GlaxoSmithKline, and for therapeutic development, including Lilly Abcellera.
- Notable other deals related to COVID-19 included funding, manufacturing collaboration and advance purchase agreements.
- The level of collaborative R&D deal-making should also remain high thanks to a steady stream of COVID-19 alliances targeting the development of next-generation therapeutics and vaccines, such as the February 2021 deal between GSK and CureVac to co-develop next-generation mRNA vaccines for COVID-19 with the potential for a multivalent approach to address multiple emerging variants in one vaccine. This kind of research and the type of deal structure are both likely to be a feature of the next several years.

Emerging biopharma companies are responsible for most of the late-stage pipeline, though their share fell in 2020

Exhibit 35: Percent of Late-Stage Pipeline by Company Segment, 2005, 2010, 2015, 2020



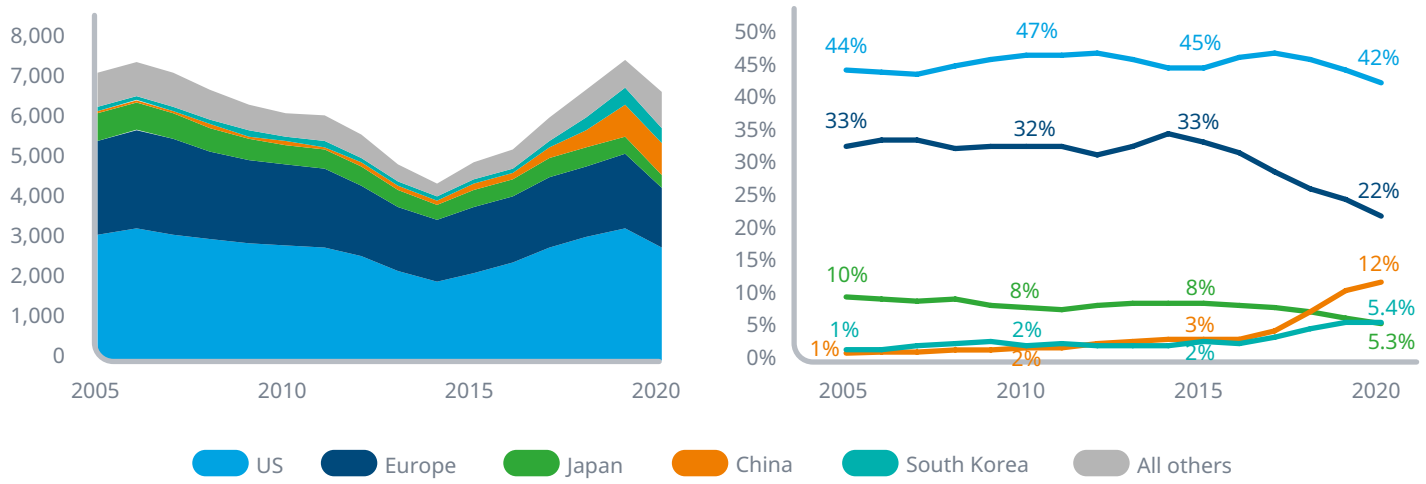
Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Mar 2021

- The contribution of emerging biopharma companies - defined as those with less than $500 million in annual sales and R&D spending less than $200 million per year - has expanded steadily over the past 15 years and was 64% of the total late-stage pipeline in 2020.
- Large pharma companies have seen their share fall from 34% in 2005 to 24%, even though the absolute number of drugs they have developed has increased by about 40% - from 554 in 2005 to 785 in 2020.
- In total, there are more than 3,000 emerging biopharma companies with active research programs and 15 large pharma companies, defined as those with greater than $10 billion in annual global sales.
- The share of the late-stage pipeline owned by emerging biopharma companies dropped 3 percentage points in 2020 from 2019 as some were impacted by COVID-19 disruptions, causing their research programs to become inactive.
- As some drug programs can involve collaborations, partnerships and co-development by companies of different sizes, this analysis applies the company segment of the larger company to each drug, and as such drugs associated with emerging biopharma are being developed alone or with other emerging companies.

Exhibit Notes: Includes drugs with an active research program, with phase determined by the highest phase of research regardless of indication. Company segment when two or more companies are involved is determined by the larger sales segment.

Drugs from China-headquartered companies have risen to 12% of the early-stage pipeline from 2% a decade ago

Exhibit 36: Number of Drugs Over Time and Country Share of Early-Stage Pipeline Based on Company Headquarter Location 2005-2020



Source: IQVIA Pipeline Intelligence, Dec 2020; IQVIA Institute, Apr 2021

- The U.S. share of global early-stage R&D has remained relatively stable over the past 15 years.
- Europe's share has declined from 33% to 22% over the past five years, while the absolute number of active programs declined by 175 — from 1,604 to 1,429.
- Products from China-headquartered companies now represent 12% of the early-stage pipeline, up from 3% five years ago and 1% in 2005.
- South Korea now represents 5.4% of the early-stage pipeline, up from 2% five years ago and 1% in 2005, and notably now larger than those from Japan-headquartered companies.
- Companies headquartered in Japan have seen a declining share of the early-stage pipeline, dropping to 5.3% in 2020, down from 8% five years ago and 10% in 2005.

Exhibit Notes: Includes drugs with an active research program, with phase determined by the highest phase of research regardless of indication. Corporation nationality of all participating companies is assessed for each product. Due to co-development of products by companies from different geographies, shares are overlapping and the total products across countries exceeds the total active early-stage pipeline. Europe is defined as any country in continental Europe.

New drug approvals and launches

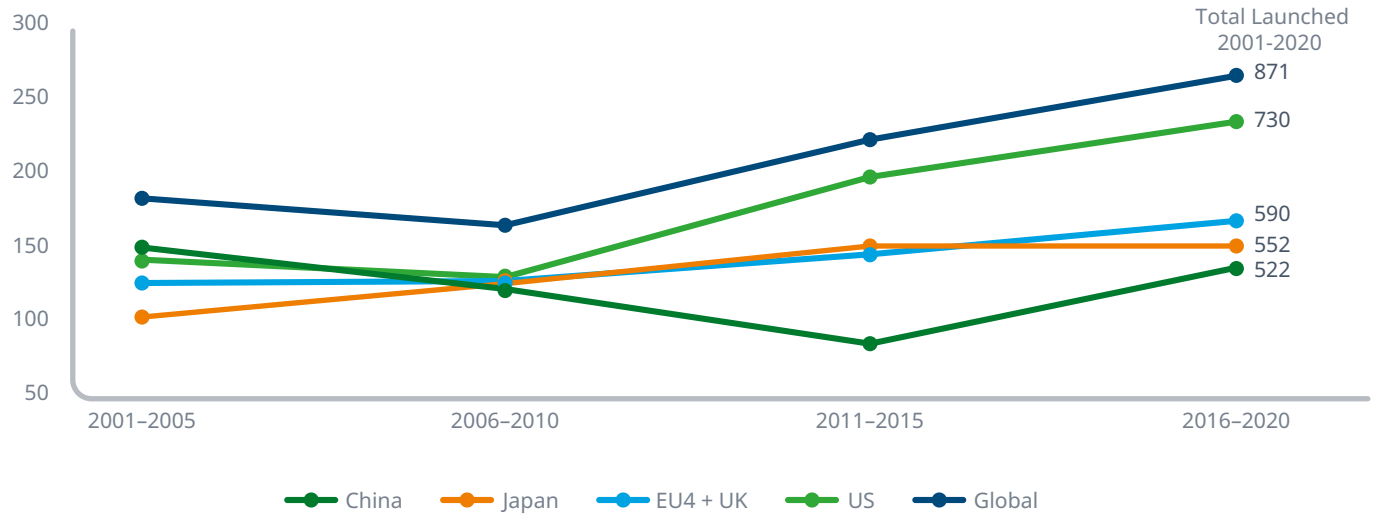
Sustained investment and efforts to discover and develop innovative medicines by small and large companies yielded a record 66 new drugs globally, with particular success in oncology and treatments for rare diseases.

- The total number of new active substances (NAS) launched for the first time in 2020 reached an all-time high of 66 globally and in the U.S. remained above 50 for the third consecutive year, reflecting strong growth since 2010 when 25 NASs were launched globally and 24 were launched in the U.S.
- In the U.S., oncology, neurology and infectious diseases – including COVID-19 vaccines launched under Emergency Use Authorization – made up 73% of total new launches in 2020.
- The discovery and development of medicines for small patient populations and which receive orphan drug designation from the U.S. Food and Drug Administration resulted in 31 new orphan drugs launched in 2020, including 18 first-in-class and 26 approved based on a Phase I or II trial.
- Racial and ethnic diversity in clinical trials remains a challenge, with more than half of trials under-representative of key groups.
- The mix of new drugs in 2020 include more receiving expedited reviews, breakthrough designations and more diverse trial designs.
- The median time from patent filing to product launch for NASs fell to 10.7 years in 2020, down from 16.1 years in 2016 and the shortest time since 2002.
- Emerging biopharma companies originated and launched 40% of NAS in 2020, slightly lower than in the prior two years but significantly higher than historic levels as more companies remain independent through the development and launch of their innovative medicines.
- Development partners and pathways were diverse for the successful approvals and launches in 2020, with those that originated with emerging biopharma or were launched by them accounting for 35 of the 55 NAS launched in the U.S., some with multiple changes of ownership or participation and a diverse set of critical regulatory events.

The total number of new active substances (NAS) launched for the first time in 2020 reached an all-time high of 66 globally and in the U.S. remained above 50 for the third consecutive year.

A total of 264 new active substances have launched globally in the past five years, bringing the 20-year total to 871

Exhibit 37: Number of New Active Substances Launched Globally and in Selected Countries



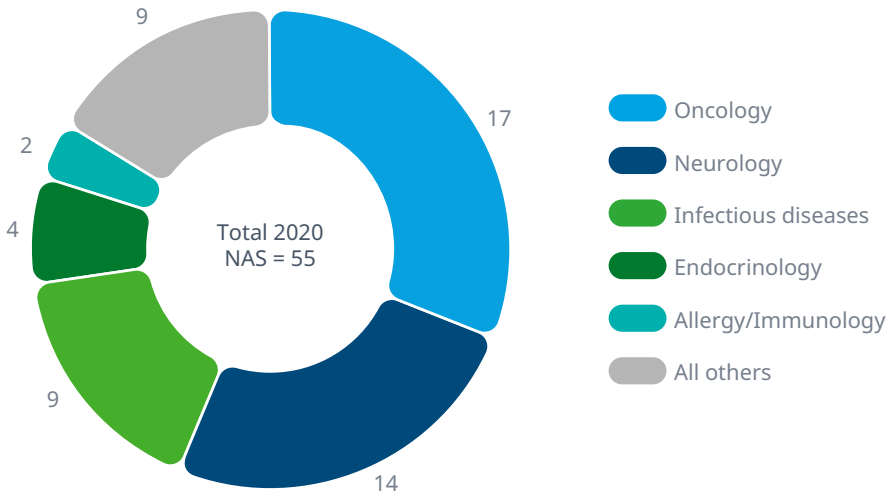
Source: IQVIA Institute, Apr 2021

- A total of 66 new active substances have launched globally in 2020, bringing the five-year total to 264.
- Global NAS launches reached 66 in 2020, the highest ever total, including the emergency use authorizations (EUA) for vaccines and therapeutics for COVID-19.
- The U.S. FDA approved 55 NAS and a total of 55 NAS launched in 2020, including the EUAs for COVID-19 vaccines and therapeutics, the third consecutive year over 50 NAS launches.
- The European Medicines Agency approved 39 NAS in 2020, with 35 confirmed launches from the four largest EU member countries (France, Germany, Italy, Spain) and the U.K.
- Japan had 31 NAS launches in 2020, the ninth consecutive year with 25 or more launches, and is continuing to launch medicines sooner after global launch than earlier in the century.
- China's NMPA approved 49 NAS in 2020, with 31 confirmed to have launched before the end of the year, and with the high numbers driven by regulatory acceleration mechanisms from NMPA, such as breakthrough and orphan designations, priority reviews, and reimbursement reforms encouraging earlier application by multinationals who are making up a larger share of launches than in earlier years.
- The outlook for the next five years includes almost 300 NAS launches globally, up 15% from the past five years, and shifting to more specialty, niche and rare disease treatments.

Exhibit Notes: Novel active substance (NAS) is defined as a medicine with at least one novel ingredient and is noted in the year it launches for the first time in the relevant geography. Fixed-dose combinations are NAS if one of the ingredients is novel, but are not if both are previously available. Emergency use authorizations (EUA) are counted as NAS in the year the medicine became available to patients and no exclusion is applied for approval type. COVID-19 vaccines are counted as NAS based on the technology used to create them, with those made by mRNA technology counted as one NAS, and those made by other means as another NAS.

Oncology, neurology and infectious diseases made up 73% of NAS launches in the U.S.

Exhibit 38: New active substances (NAS) launched for the first time in the United States in 2020



Source: IQVIA Institute, Mar 2021

- Combined oncology, neurology and infectious diseases accounted for 40 of the 55 NAS launches in 2020.
- The most notable U.S. NAS launches in 2020 were the three emergency use authorizations for two COVID-19 vaccines and one therapeutics, appearing on the market in the same year as the start of the pandemic.
- Oncology had 17 NAS launches in 2020, 16 of which were orphan drugs, and the fourth consecutive year in double-digits, bringing the five-year total to 62, or 27% of the five-year launch total of 233.
- Neurology had 14 launches including four migraine drugs, other rare neurology treatments, and an imaging agent for Alzheimer's disease.
- Infectious diseases had nine new drugs including three emergency authorizations for COVID-19 and two for Ebola virus.
- Infectious diseases have been a rising focus in recent years as global philanthropy has brought a focus to neglected tropical diseases alongside the research for HIV, hepatitis C, and complicated infections.
- It is notable that one of the COVID-19 launches, remdesivir, was in studies for hepatitis C, Ebola and Marburg viruses before being found to have efficacy for COVID-19.

Exhibit Notes: Oncology includes therapeutics, and does not include three imaging agents for cancers which are included in the all other category; Neurology includes diagnostics.

New medicines launched in 2020 included 31 orphan drugs

Exhibit 39: New Medicines Launched in 2020 in the United States

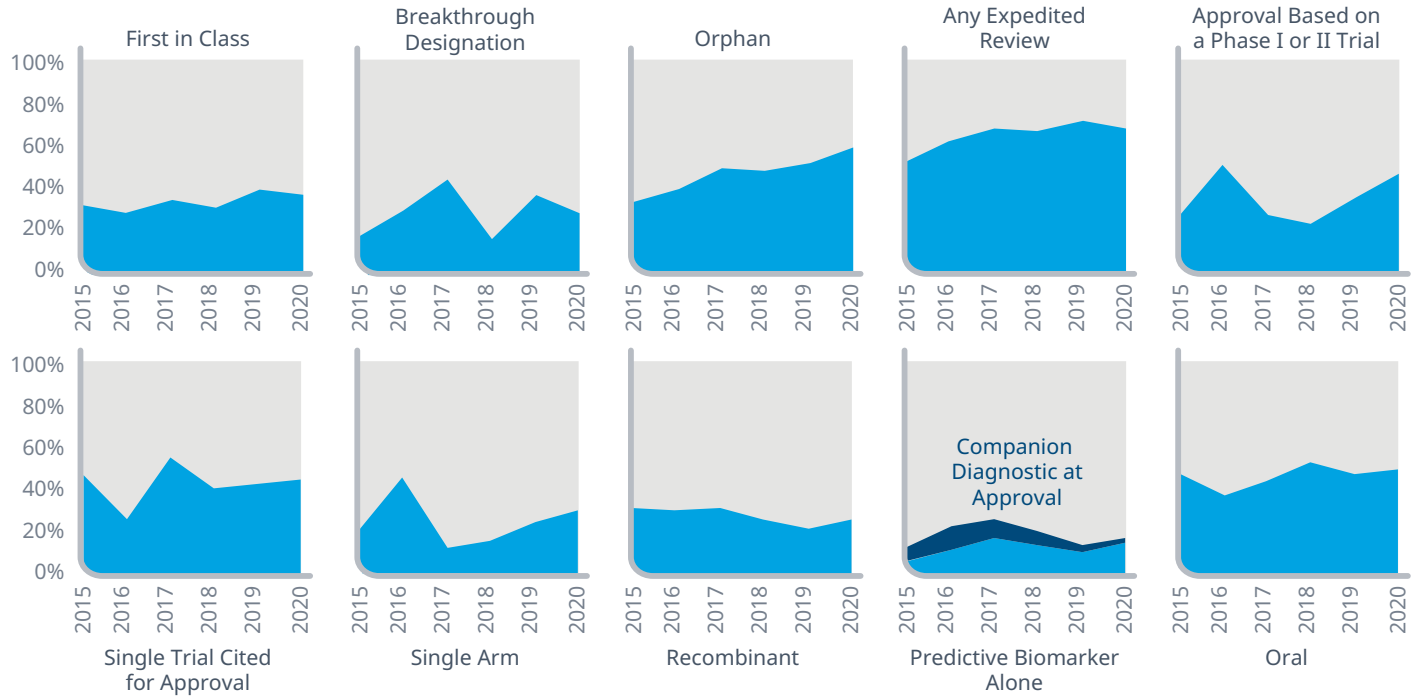
*ATTRIBUTES KEY: 1 = Oral, 2 = Biotech (Recombinant), 3 = Predictive biomarker, 4 = Companion diagnostic at approval, 5 = Approval based on a Phase I or II trial, 6 = Single arm, 7 = Single trial cited for approval, 8 = Multi-indication at approval, 9 = Orphan, 10 = First in Class

THERAPY AREA	INDICATION	BRAND	MOLECULE	ATTRIBUTES*									
				1	2	3	4	5	6	7	8	9	10
Oncology	Cholangiocarcinoma	Pemazyre	pemigatinib	●		●		●	●	●		●	
	Diffuse large B-cell lymphoma	Monjuvi	tafasitamab-cxix		●			●	●	●		●	●
	Epitheliod sarcoma	Tazverik	tazemetostat	●				●	●	●		●	●
	Gastrointestinal stromal tumors	Ayvakit	avapritinib	●		●		●	●	●		●	
		Qinlock	ripretinib	●						●		●	
	HER2+ breast cancer	Enhertu	fam-trastuzumab deruxtecan-nxki		●	●		●	●				
		Tukysa	tucatinib	●				●		●		●	
	Mantle cell lymphoma	Tecartus	brexucabtagene autoleucel		●			●	●	●		●	
	MET exon 14 skipping NSCLC	Tabrecta	capmatinib	●		●	●	●	●	●		●	
	Multiple myeloma	Blenrep	belantamab mafodotin		●			●		●		●	●
		Sarclisa	isatuximab		●					●		●	
	Myelodysplastic syndrome (MDS) or chron myelomonocytic leukemia (CMML)	Inqovi	decitabine and cedazuridine	●				●			●	●	
	Neurofibramotosis 1	Koselugo	selumetinib	●				●	●	●		●	●
	RET-mutated NSCLC	Gavreto	pralsetinib	●		●		●	●	●		●	
	RET-mutated NSCLC and thyroid cancer	Retevmo	selpercatinib	●				●	●	●	●	●	
	Small cell lung cancer	Zepzelca	lurbinectedin					●	●	●		●	
	Triple-negative breast cancer	Trodelvy	sacituzumab govitecan-hziy		●			●	●	●		●	
Neurology	AQP4+ neuromyelitis optica spectrum disorder (NMOSD)	Uplizna	inebilizumab-cdon		●	●		●		●		●	●
		Enspryng	satralizumab-mwge		●	●						●	●
	Duchenne musc dystrophy (DMD)	Viltepso	viltolarsen			●		●				●	
	Insomnia	Dayvigo	lemborexant	●									
	Migraine	Vyepti	eptinezumab-jjmr		●								
		Nurtec	rimegepant	●						●			
		Ubrelvy	ubrogepant	●				●					
		Reyvow	lasmiditan	●									●
	Multiple sclerosis	Zeposia	ozanimod	●									
	Non-opioid pain management	Olinvyk	oliceridine										
	Parkinson's disease	Ongentys	OPICAPONE	●									
	partial-onset seizures in adults	XCOPRI	cenobamate	●				●					
	Spinal muscular atrophy	Evrysdi	risdiplam	●				●				●	
	Tau imaging for Alzheimer's	Tauvid	flortaucipir F18						●				●
Infectious diseases	Complicated urinary tract infection	Fetroja	cefiderocol					●		●			
	Ebola virus	Ebanga	ansuvimab		●			●		●		●	
		Inmazeb	atoltivimab, maftivimab, and odesivimab-ebgn		●			●		●		●	●
	HIV	Rukobia	fostemsavir	●						●			●
	COVID-19	Veklury	remdesivir										●
		Cominarty	Vaccine, COVID-19 mRNA										●
		LY-COV555	bamlanivimab		●								●
		Regen-COV	casirivimab + imdevimab		●								●
	Malaria	artesunate	artesunate	●								●	
All others	Cushing's disease	Isturisa	osilodrostat	●						●		●	●
	Long-chain fatty acid oxidation disorders (LC-FAOD)	Dojolvi	triheptanoin	●				●				●	
	Primary hyperoxaluria type 1	Oxlumo	lumasiran						●			●	●
	Thyroid eye disease	Tepezza	teprotumumab-trbw		●			●				●	●
	Detection of Breast cancer	Cerianna	fluoroestradiol F18						●				
	Detection of NET tumors	Detectnet	copper Cu 64 dotatate injection						●			●	
	PET imaging for prostate cancer	gallium 68 PSMA-11				●							●
	Hereditary angioedema	Orladeyo	berotralstat	●						●		●	
	Peanut allergies	Palforzia	Peanut (arachis hypogaea) allergen powder	●									●
	Familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD)	Nexletol	bempedoic acid	●							●		●
	Anti-emetic	Barhemsys	amisulpride	●									
	Erythropoietic protoporphyria	Scenesse	AFAMELANOTIDE									●	●
	Stain for internal limiting membrane	TissueBlue	Brilliant Blue G Ophthalmic Soln									●	
	Schizophrenia	Caplyta	lumateperone tosylate	●				●					
	Infertility	ExEm Foam	air polymer-type A										
Totals				27	14	9	1	26	16	23	3	31	21

Source: IQVIA Institute, Apr 2021

The mix of new drugs in 2020 included more receiving expedited reviews, breakthrough designations and more diverse trial designs

Exhibit 40: U.S. NAS Launches by Characteristics of Approval 2015–2020



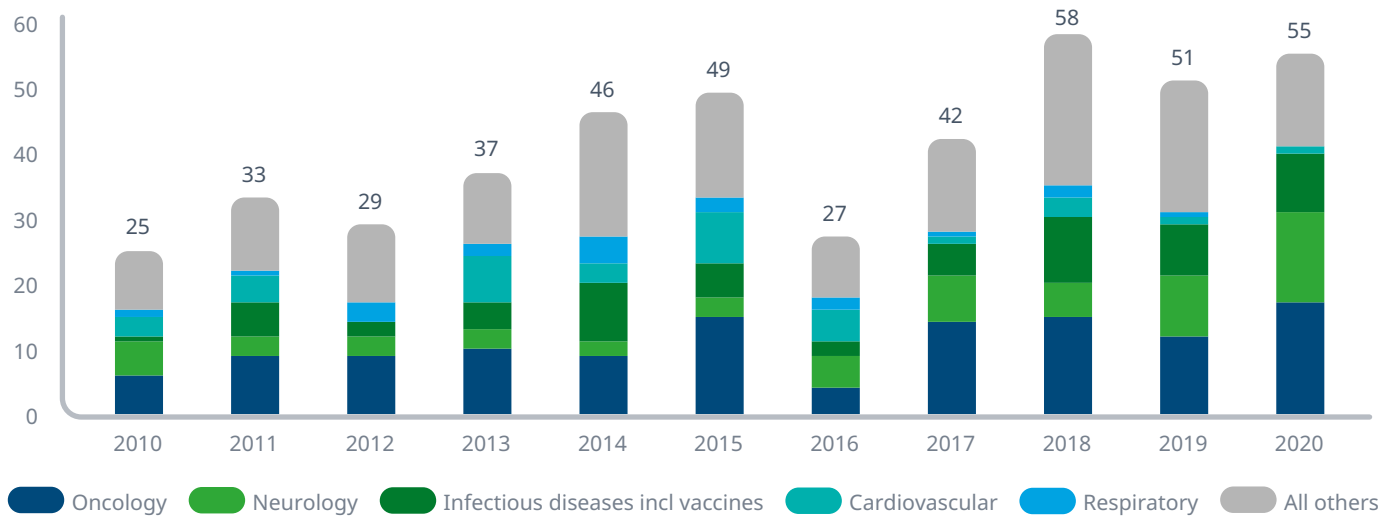
Source: IQVIA Institute, Apr 2021

- New launches in the past six years have demonstrated diverse trends across specialized attributes relating to their novelty, form, approval pathway, and nature of evidence.
- New launches included 16 breakthrough designations and for a total of 72 in the past five years, often being approved from earlier-phase trials more rapidly than traditional pathways.
- The focus on discovery and development of medicines for patients with rare diseases has yielded 31 in 2020 and more than 100 in the past four years.
- Drugs which were the first-in class of a novel mechanism included 21 drugs continuing a steady upward trend in the past five years.
- Increasingly, approvals have some form of expedited review, the most notable of which were the review periods for COVID-19 vaccines, which received emergency authorizations within a month of submission of their application.
- Many of the medicines over the past six years have been approved based on relatively limited trial evidence, few study subjects, in single trials with a single study arm, and based on their demonstrated evidence in earlier phase trials.
- As a result, this collective group of products is increasingly being monitored more thoroughly after launch with registries, REMS (Risk Evaluation and Mitigation Strategies) programs, real world evidence (RWE) studies, and in some cases, approvals are being revisited by the FDA, which could result in a more limited indication or revocation of the approval.

Exhibit Notes Exhibit Notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States 2015-2020 regardless of the timing of FDA approval. Orphans include drugs with one or more orphan indications approved by the FDA at product launch. Products are not reclassified as orphan if they subsequently receive an approval for an orphan designated indication.

Oncology, neurology and treatments for bacterial, viral or fungal infections had 58% of NAS launches in the past five years

Exhibit 41: U.S. Launches of Novel Active Substances (NAS) by Therapy Area 2010–2020



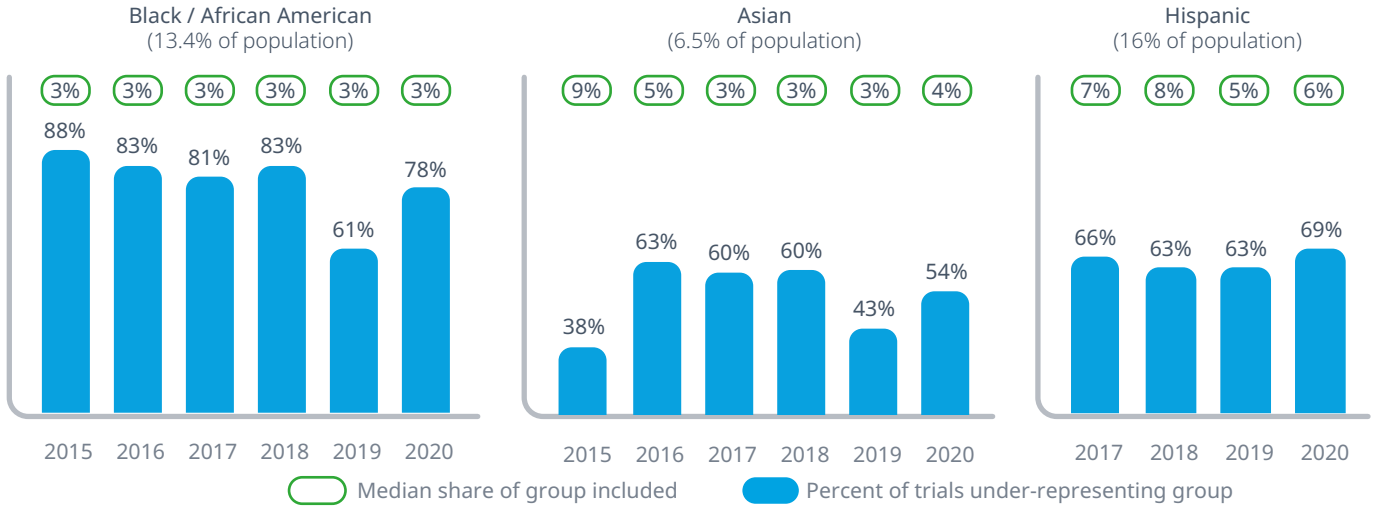
Source: IQVIA Institute, Apr 2021

- Oncology, neurology and infectious diseases have all had a rising share of new launches in the past five years with 136 of the 233 launches (58%), compared to 91 of 194 (39%) from 2011 to 2015.
- The total 114 new oncology launches in the past decade includes some of the most groundbreaking new treatments in immuno-oncology as well as next-generation biotherapeutics, and many treatments for rare cancers.
- Neurology includes 54 drugs in 10 years, and many of the more recent launches are for rare neuromuscular diseases as well as the new CGRP mechanism for migraine treatment, the first new mechanism for migraines in decades.
- Infectious diseases, including antibacterial, antiviral, antifungal and antiparasitic treatments, have included treatments for neglected tropical diseases such as malaria, tuberculosis, and more recently, Ebola.
- Other infectious disease treatments include the highly impactful cluster of novel hepatitis C treatments launched since 2013.

Exhibit Notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States by year regardless of the timing of FDA approval.

Racial and ethnic diversity in clinical trials remains a challenge, with more than half of trials under-representative of key groups

Exhibit 42: Percentage of Trials Under-representative of Racial/Ethnic Groups in the U.S. and the Median Share (%) of Subjects Included in Trials by Racial/Ethnic Group Per Year, 2015–2020



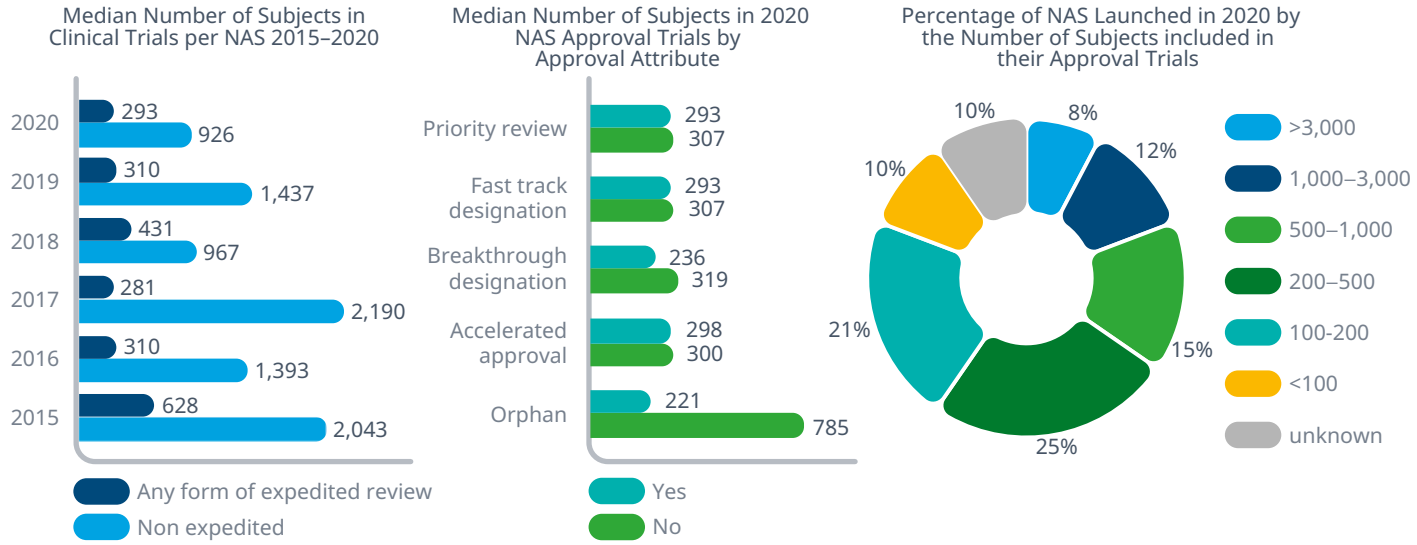
Source: FDA Drug Trials Snapshots 2015-2020, Accessed Apr 2021, Available at: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

- African Americans or races identified as Black account for 13.4% of the U.S. population while the clinical trials used to approve new medicines had a median participation of only 3% in the past six years, and were under-representative 79% of the time from 2015 to 2020.
- Persons of Asian descent are estimated to comprise 6.5% of the U.S. population, but only in 2015 was the median above this threshold, and 52% of trials in the past six years that were used by the FDA to approve medicines had under-representative participation.
- Hispanic or Latino ethnicity is estimated at 16% of the U.S. population, and consistently the median participation in trials is less than half that level, though patients may not always identify themselves.
- Racial or ethnic equity in trials is difficult to assess, however, because many trials are global.
- Several trials for tuberculosis, sickle cell anemia, beta thalassemia and HIV in 2019 had very high Black or African trial subjects for logical clinical or epidemiological reasons, leading to greater representation that year.
- For trials during the COVID-19 pandemic, some have under-represented the Black / African American population while including more Hispanic participants than the U.S. overall.

Exhibit Notes: FDA drug trial snapshot summaries include summary demographics for pivotal trials used in approvals that year, statistics include the percentage of trial participants of various demographic attributes if that information was included in the trial and disclosed. FDA reports did not include Hispanic racial/ethnicity details in 2015 and 2016. Series shown are only those trials with racial/ethnic representation below the U.S. national population of the group.

Recent approvals are often with forms of expedited review, including relatively few subjects

Exhibit 43: Number of Subjects Included in NAS Approval Trials by NAS Expedited Review Status and Type



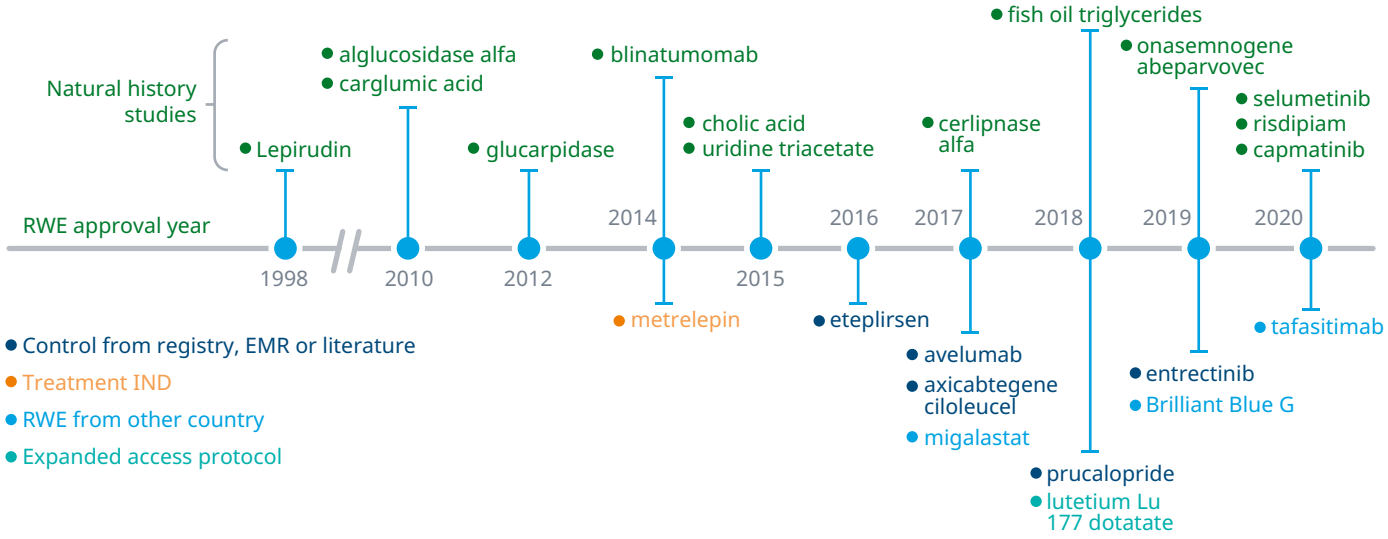
Source: IQVIA Institute, Mar 2021

- Of the 52 approved NAS in 2020, excluding emergency use authorizations, only 20% had more than 1,000 patients in their trials, which is an increasingly common issue.
- Consistently, drugs approved through some form of expedited review have a lower median number of subjects, while the key difference in enrollment appears to be from drugs with a breakthrough designation or orphan status.
- Of the 31 orphan NAS launched in 2020, the median participants was 221, compared to the 21 non-orphan NAS with 785 subjects.
- Notably, priority review, fast track and accelerated approval do not appreciably change the trial population in the studies observed in 2020.
- The number of subjects included in a trial is a function of having enough subjects to demonstrate the benefit and risk profile of the treatment to satisfy the regulator. The downward trend reflects how many drugs are treating small populations with large unmet needs and receiving the associated regulatory latitude to enable trials to progress quickly.

Exhibit Notes: Expedited review includes accelerated approval, priority review, breakthrough therapy, and fast track designations; orphan drug designation is not included.

The use of real world evidence is increasingly part of regulatory submissions and included in the approval decisions from the FDA

Exhibit 44: Timeline of U.S. FDA NAS Approvals Based on Real World Evidence (RWE)



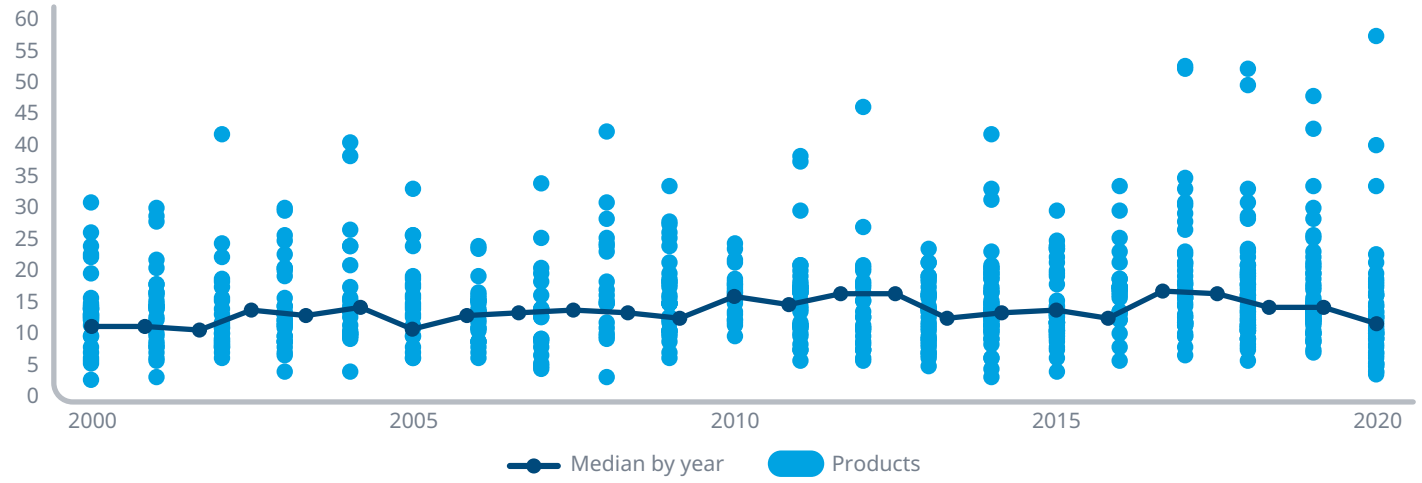
Source: IQVIA Institute, Feb 2021

- As the FDA continues to explore and support the use of the totality of evidence, the rising use of RWE is notable. The use of RWE is increasingly submitted by companies, and some of that evidence is deemed influential; a smaller portion of it is deemed supportive evidence for the approval and/or findings referenced in the package insert.
- Submissions include things like natural history studies, analyses of electronic medical records or registries, or the data from treatment in other countries where the drug had been approved earlier than in the U.S.
- The most common type of RWE to be considered in approvals is commonly natural history studies, with six in the past five years.
- Use of control arms from registries, EMR data or literature has also been used to approve six drugs over the past five years.
- RWE from other countries has been part of the approval for three drugs in the last three years, mostly for rare conditions.
- RWE has been used from expanded access protocols or from treatment INDs, which have each been used once to make later approvals for those drugs.

Exhibit Notes: Collected from public sources relating to the approval trials for medicines. 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. Analysis does not include: RWE approvals for Ibrance (Palbociclib), Kalydeco (ivacaftor), NovoSeven (coagulation Factor VIIa, recombinant), Methylene Blue (methylthioninium chloride), thiotepa, or Risperidone Consta (paliperidone palmitate), as either the approval was a supplementary approval or the medicines were not NAS when approved.

The median time from patient filing to product launch for the 2020 NAS cohort fell to 10.7 years in 2020, the shortest time since 2002

Exhibit 45: Median Time from First Patent Filing to Launch by NAS Launch Year, United States

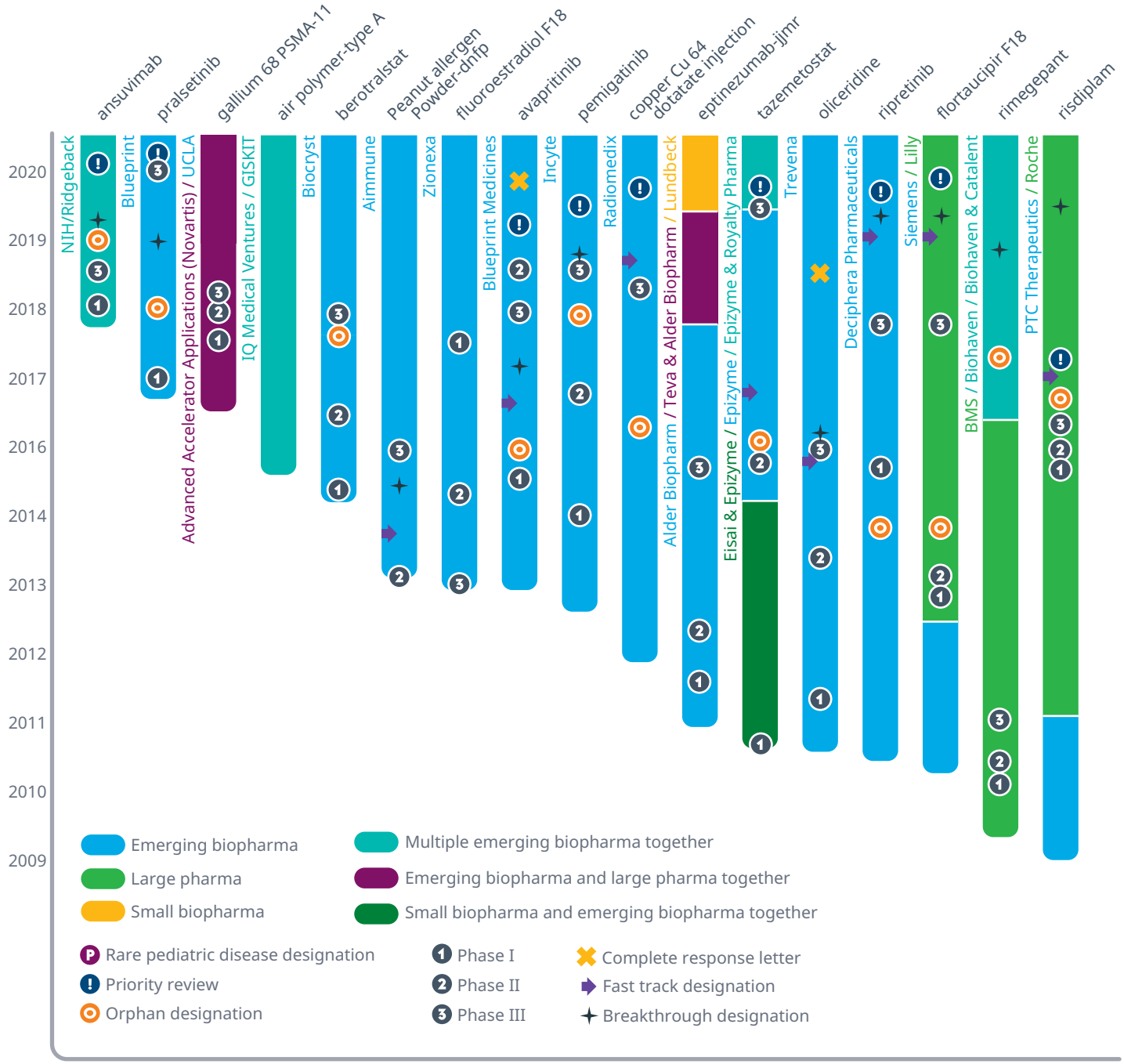


Source: IQVIA ARK Patent Intelligence, IQVIA Institute, Mar 2021

- The time between the first patent filing for a drug and the launch into the market represents an important assessment of the amount of protected life remaining when a product launches.
- As some accelerated approval pathways shorten approval times, this measurement of elapsed time provides insight into whether the acceleration changes these other dynamics of a product's lifecycle.
- The median time to launch for the 2020 cohort represents the shortest timeframe since 2002, even as the cohort includes significant outliers with longer durations.
- Amisulpride, for post-operative nausea, was actually first developed and marketed in other countries as an antipsychotic medicine, and while it is an NAS in the U.S., the patents for new indications such as this typically do not provide protection for as long as product patents.
- Drugs with very long durations from first patent to launch typically have a similar pattern and will likely only have market exclusivity for the new active substance status in the U.S. or other weaker patents and a shorter protected life.
- Excluding the long timeframe outliers, drugs still appear to be reaching the market marginally more quickly than in previous years.

Products originated with emerging biopharma or launched by them had a diverse set of lifecycle events including changes in ownership

Exhibit 46a: Pathways to Launch for Products Originated by or Filed with FDA by Emerging Biopharma Companies

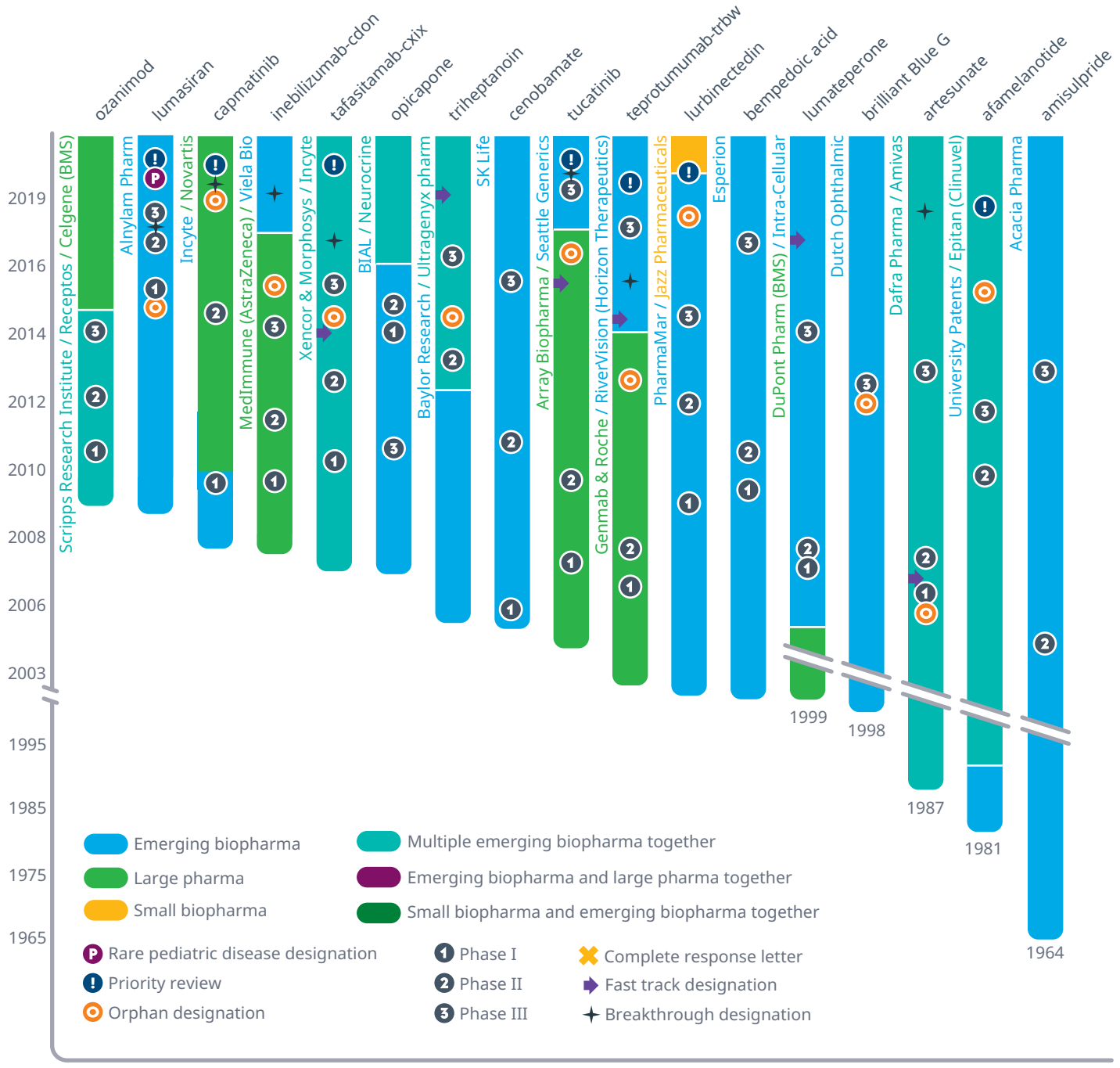


Source: IQVIA Patent Intelligence; IQVIA Pipeline Intelligence; IQVIA Institute, Mar 2021

Chart notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new. Designations flagged are FDA designations including rare pediatric, fast track, breakthrough, and orphan. Priority review are noted when they were announced. Phase I, II, III start have been included where identified as the first phase start across indications and geographies. Submission is based on the date companies announced filing with the FDA. Complete response letters are provided by FDA as a conclusion to an application, but allow the applicant to resolve the issues and resubmit. Companies who jointly filed with FDA have been indicated with combined coloring in the legend.

Some products launched by emerging biopharma companies were older medicines never previously launched in the U.S. and given new uses

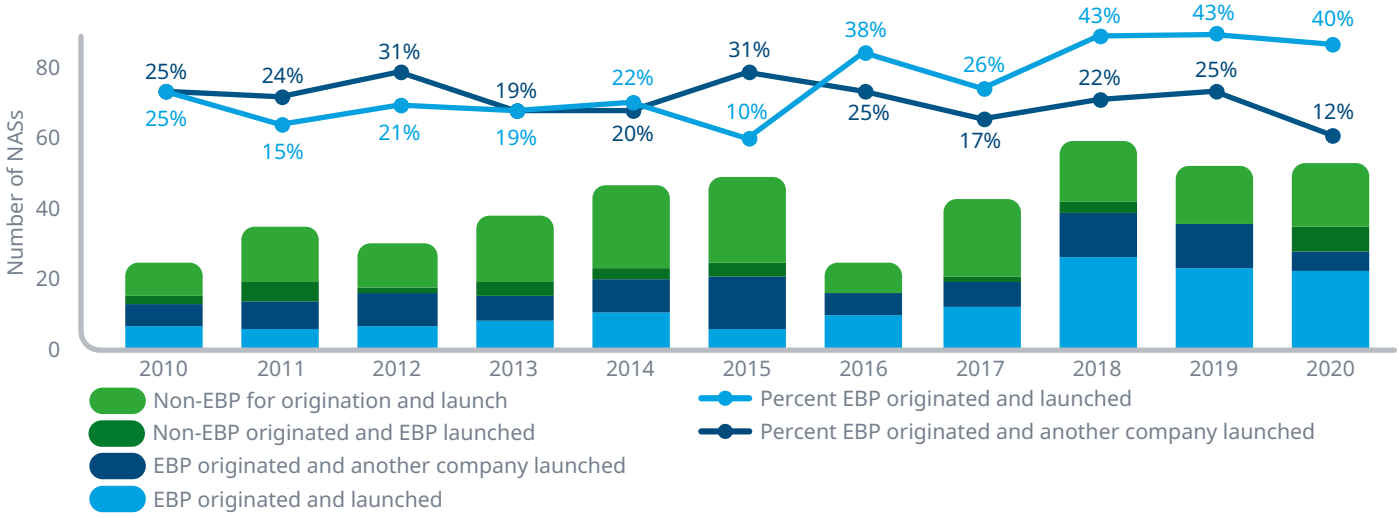
Exhibit 46b



Source: IQVIA Patent Intelligence; IQVIA Pipeline Intelligence; IQVIA Institute, Mar 2021

Emerging biopharma companies originated and launched 40% of all new drugs in 2020, reflecting greater independence in development activities

Exhibit 47: Companies Originating and Filing FDA Regulatory Submissions for NASs and Percent of Launches by NAS Launch Year



Source: IQVIA Institute, Dec 2020

- The development of new medicines commonly has a very large share by larger companies, and that is bolstered by the acquisition of companies and/or products over time.
- That traditional patterns is largely changed in recent years with the last three years having over 40% of NAS originated and launched by emerging biopharma companies (those with less than $500 million in sales and less than $200 million in R&D spend per year).
- Furthermore, these emerging biopharma companies (EBP) have only been the originator for a further 12% of NAS this year, increasingly marketing their developments themselves.
- The group of products developed by non-EBP companies was 25 of the 52 NAS launched in 2020, or 48% and 41% of the last five years, respectively.

Exhibit Notes: Adapted from the IQVIA Institute, "Emerging Biopharma's Contribution to Innovation", May 2019; exhibit contains updates to the total number of NAS in 2018 since first published.
Emerging biopharma are companies with less than $500 million in global sales and less than $200 million in R&D spending per year. Companies origination and launch are based on research for each product and do not reflect acquisition of products/companies after launch. Furthermore, if a company is partnering for a launch but retained the filing rights and was the sponsor of a product with FDA, they are considered the launch company

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 more than 40,000 drugs and more than 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 in more than 130 countries and including more than 3,000 molecules. Research covers approved patent extensions in 51 countries, and covers all types of patents including product, process, method of use and others

IQVIA NEW PRODUCT INTELLIGENCE is a database of more than 500,000 products with distinct trade names, from launches dating back more than 30 years covering more than 60 major markets. The database reports on more than 1,500 new launches every month, and the service provides insights on which companies are successful at launching products quickly, whether releasing a brand new chemical entity or the generic version of a drug that has lost patent protection.

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.

THIRD-PARTY INFORMATION:

CITELINE'S TRIALTROVE provides intelligence about the drug development pipeline and information on clinical trials globally. Citeline reports that Trialtrove uses over 40,000 sources including ones in the public domain, and is supported by experienced industry analysts. The database includes extracted information including protocol details, as well as additional industry-relevant search terms such as its proprietary patient segments, trial outcomes and biomarker tags. It includes information on trial design, eligibility criteria, endpoints, sites, sponsors as well as anticipated and actual start and end dates as available. These attributes have been leveraged extensively in the IQVIA Clinical Productivity Index. For more information on Trialtrove see www.pharmaintelligence.informa.com/clinical-trial-data

Methodologies

SUCCESS RATES

Using IQVIA Pipeline Intelligence, which includes event dates for a comprehensive range of drug development stages where disclosed or able to be determined by editorial staff, phase start dates were tracked for each product. A phase was considered successful if there any subsequent phase has a later phase start date. In the absence of a subsequent phase start, the highest date for a negative event such as discontinuation, suspension, withdrawn by applicant, or inactive for greater than three years was examined. Analysis was conducted across all indications and considers success or failure at the drug level and so did not track a specific indication for each drug but rather measured the success of the overall program.

Overall, 30,825 distinct drugs were examined for 154,125 potential phase transitions for events from 1977 to the present. We then focused on products where the phase transitions were completed between 2010 and 2020, with valid information regarding phase transitions, either successful or failed, which includes 7,665 distinct drugs and 11,553 phase transitions.

We consider the earliest date a drug entered each phase. We consider the latest date for negative event outcomes. Negative outcomes include discontinued, suspended and withdrawn which are noted in the data collection when the sponsor discloses it. Negative events also include inactivity which is determined when there is no verified activity for three years. Inactive records are assigned to the year inactivity was determined (last time record was active plus three years).

Phase II trials includes Phases II, I/II, II, IIa and IIb. Phase III includes Phase II/III and III.

Due to unusual and unprecedented events in 2020 thought to be related to COVID-19, a larger than historic average number of drugs became inactive, i.e., reached the three-year period of inactivity. In this methodology, a drug becoming inactive during a year would be considered a failure. To adjust for the unusual pattern in 2020, an inactivity adjustment has been applied using the average number of failed drugs per year from 2015-2019 as the basis for the 2020 phase and composite success rates. Successful phase transitions were less impacted than the anomalous inactivity dynamic. The unadjusted view has also been provided in exhibits for transparency. We expect that most (but not all) of these drugs will become active again after the COVID-19 pandemic disruptions have been resolved. The base case rates using the inactivity adjustment provide a view of how the rates for 2020 may be restated in the future

Each phase's success rate requires:

- A relevant phase start date and any date occurring afterwards, either positive or negative.
- Success is any higher phase with a future date after the phase start date
- Failure is the absence of a successful phase transition and the presence of a discontinued, suspended, withdrawn or inactive event with a date that is after the phase-start date.

Invalid entries are excluded for the phases where they are invalid, and a drug can be invalid for some phases and valid for others:

- Drugs which have higher phase entries but dates are in the past. This can be an artefact of a drug with multiple indications with incomplete information for some of the indications in the source database.
- Drugs which have no higher positive phase dates, but have negative phase dates, but those dates are prior to the target phase start date. This can be an artefact of the original data being indication phase-based.

About the authors

MURRAY AITKEN
Executive Director,
IQVIA Institute for
Human Data Science

Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.

MICHAEL KLEINROCK
Research Director,
IQVIA Institute for
Human Data Science

Michael Kleinrock serves as research director for the IQVIA Institute for Human Data Science, setting the research agenda for the Institute, leading the development of reports and projects focused on the current and future role of human data science in healthcare in the United States and globally. Kleinrock leads the research development included in Institute reports published throughout the year. The research is focused on advancing the understanding of healthcare and the complex systems and markets around the world that deliver it. Throughout his tenure at IMS Health, which began in 1999, he has held roles in customer service, marketing, product management, and in 2006 joined the Market Insights team, which is now the IQVIA Institute for Human Data Science. He holds a B.A. degree in History and Political Science from the University of Essex, Colchester, UK, and an M.A. in Journalism and Radio Production from Goldsmiths College, University of London, UK.

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.

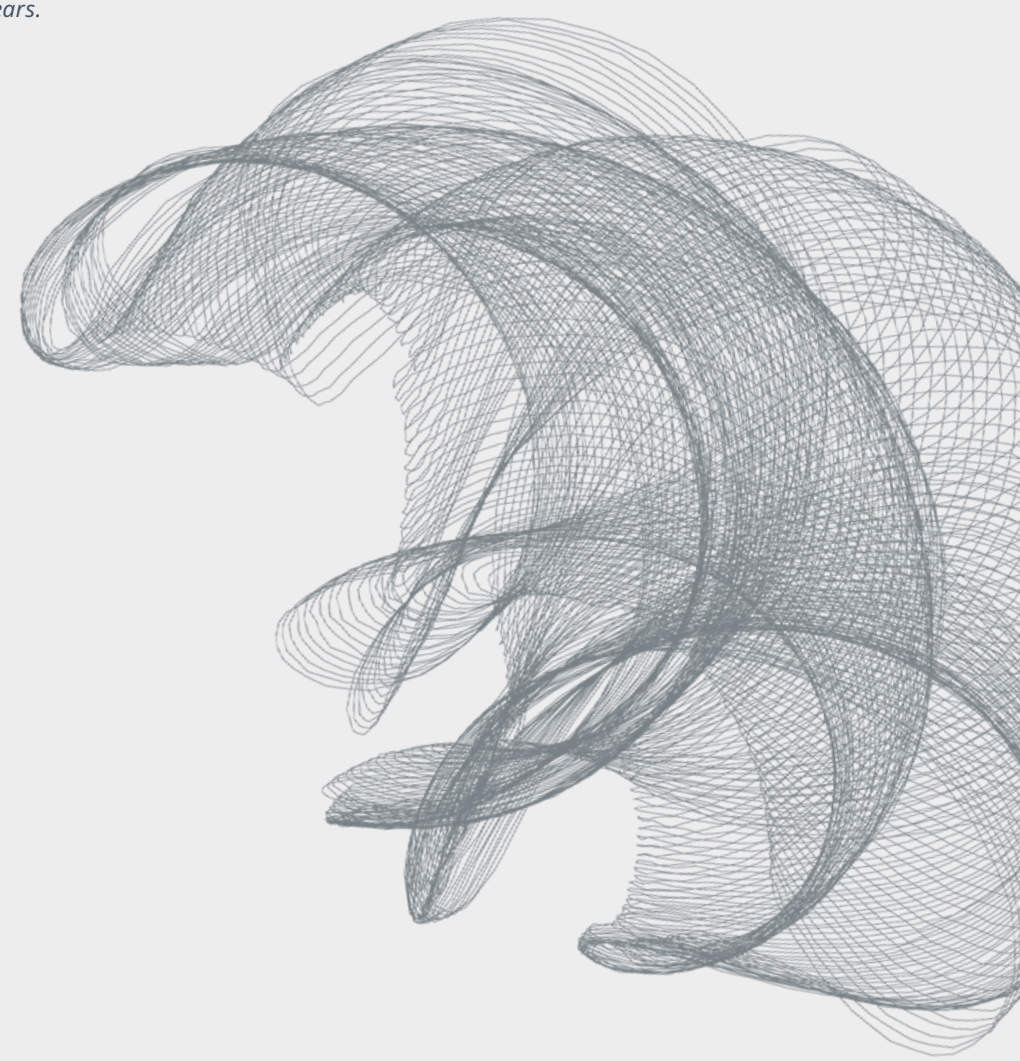
Guiding Principles

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.

This algorithmic art is based on the IQVIA Institute Clinical Productivity Index, including 10 diseases and indices of trial complexity and duration and R&D success rates over the past five years.



IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

CONTACT US
100 IMS Drive
Parsippany, NJ 07054
United States
info@iqviainstitute.org
iqviainstitute.org