

APRIL 2019

The Changing Landscape of Research and Development

Innovation, Drivers of Change, and Evolution
of Clinical Trial Productivity



Introduction

The development of innovative medicines has evolved dramatically over the past decade. As advances in science, technology and data gradually find application within clinical development, the length of time trials take to complete, the resources required due to trial complexity, and likelihood of trial success are all shifting, with impacts varying by therapy area. Ongoing changes in the clinical development process has led to a record number of drug approvals in 2018, with 59 novel treatments reaching patients in the United States alone. Over the next five years, trial productivity will be heavily influenced by key trends including biomarkers, pre-screened patient pools and predictive analytics.

This study assesses the current activity within research and development (R&D), the productivity levels of the clinical development process, and how key trial-trends will transform clinical development over the next 5 years. With record numbers of new active substances (NAS) approved and launched in 2018, the current state of innovation is explored by examining the features and development path of these therapies and the companies bringing these drugs to the market. As levels of life science venture capital activity and large pharma R&D spend continue to grow, this report also examines the expanding pipeline of therapies still under development.

To examine historical and future clinical trial productivity trends across therapy areas, this report puts forth a proprietary Clinical Development Productivity Index that reflects changes in trial complexity, success and duration. A 10-year historical view of these metrics is provided and future changes to productivity through 2023 are modeled based on the IQVIA Clinical Development Trends Impact Assessment completed by IQVIA experts. Eight key trends driving change in clinical development are explored along with their expected quantitative impact on elements of productivity at a therapy area level.

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Executive summary

NEW DRUG APPROVALS AND LAUNCHES

A record number of new active substances (NAS) were approved and launched in the United States in 2018, bringing new treatment options to patients. Among these 59 NASs, 27% are new therapies to treat cancer and its symptoms and 20% are for the treatment of infectious diseases. Almost half of these therapies carried an orphan drug designation and over a third of NAS launches were identified by the FDA as first-in-class, having mechanisms of action different from those of existing therapies.

Translating a scientific breakthrough to the development of a therapeutic medicine remains a slow process, with the 2018 cohort of NASs taking a median of 13.6 years from the time of first patent filing to launch. Still, the 2018 NASs launched approximately two years faster than those in the prior two years. Among the 2018 new drug launches, 12 drugs were launched more than 20 years after their first patent filing, reflecting in some cases drugs with older mechanisms of action being repurposed and drugs that had previously launched globally but not in the United States. Over two-thirds of new drugs in 2018 came through the regulatory process under one of several tracks intended to accelerate development and review, but over the past three years only those with accelerated approval and breakthrough status have seen significantly shorter times from patent filing to launch.

Of the NASs launched in 2018, 46% were also approved based on data from trials with fewer than 500 subjects in total, as drugs types are increasingly specialty, niche and orphan drugs, which typically enroll fewer subjects. In addition, the amount of time a drug has been tested in a patient population at time of approval – patient-years at approval – is declining.

The companies bringing these drugs to the market are also changing. Emerging biopharma (EBP) companies

patented almost two-thirds of these new drugs and registered 47% of them, while large pharma companies patented one-quarter of the total. The critical role of emerging biopharma companies in sourcing innovative medicines has expanded significantly since 2010, when they registered 33% of the drugs launched that year. Although the importance of large pharma in originating molecules is decreasing, they remain important partners for EBP companies even as EBP are increasingly able to commercialize alone. Large pharma companies registered nearly half of the new drugs in 2018, approximately half of which originated with emerging biopharma companies.

CLINICAL DEVELOPMENT PIPELINE

As levels of life science investment continue to grow, the pipeline of therapies still under development similarly has been expanding. The number of molecules in late-stage development now totals 2,891, increasing 11% in 2018 and 39% over the past five years. Oncology drugs increased in number by 63% over the past five years, contributing over 40% of the total pipeline increase, while the number of vaccines under development has declined over this period by 4%. Pain and dermatology drugs also increased over 50% since 2013 but represent just under 6% of the total pipeline each. Therapy areas that have seen the biggest increase in activity over the past year are those focused on oncology, ALS and other degenerative musculoskeletal conditions, rare diseases related to the GI tract, and non-narcotic pain treatments.

Next-Generation Biotherapeutics (NGB) including cell, gene and nucleotide therapies – though they still represent less than 10% of the total late-stage R&D pipeline – have more than doubled in number over the past three years, as these new approaches to treating and curing diseases command growing attention and investment. Three NGBs were launched in 2018, and

though fewer than 20 are now available to patients, they reflect recent and growing advances and activity in oncology, neurology and rare diseases.

EBP companies, active in the fastest growing areas of oncology and orphan drugs, also accounted for 72% of the 2018 late-stage pipeline activity, up from 61% a decade ago. Large pharma companies have seen their share of the pipeline drop from 31% to 20% over the same period.

Investment in future medical innovation continued to grow in 2018 reflecting confidence in scientific innovation to tackle unmet health needs. Venture capital firms invested over \$23 billion in 2018, with a record number of deals recorded, and the 15 largest pharmaceutical companies recorded more than \$100 billion in R&D expenditure for the first time, up 32% over the past five years.

CLINICAL TRIAL ACTIVITY

The total number of clinical trials that started in 2018 similarly indicate robust R&D growth of 9% over the prior year and 35% over the past five years. Most of this increase is due to the number of Phase II trials, which increased 26% in 2018 and 61% over the level five years ago, driven by oncology and neurology trials. Clinical trials across phases in GI/NASH and oncology have increased significantly, up 42% and 27%, respectively in 2018, while trial activity in the other major therapy areas, such as endocrinology and respiratory, has declined.

The composite progression time from the initiation of Phase I clinical development for a drug until a registration decision is reached was 12.5 years in 2018, up six months from 2017, and resuming the gradual lengthening of progression time for all drugs in development. The composite success rate of clinical development from Phase I trials to regulatory

submission – based on the percent of drugs successfully progressing to each next stage of development – fell to 11.4% in 2018, down from 14.4% in 2017, and was below the average of 14% in the prior ten years. All stages of clinical development saw declines in success rates in 2018, with Phase I and Phase III trial success both falling by 7–8%. Success rates by development stage have all generally been consistent over the past decade, with 2015 an exceptional year, when the composite success rate exceeded 22%. While therapy classes and drug types under development have changed during the past decade, oncology has had slightly lower composite success rates (12%) than non-oncology (14.1%).

To examine the productivity of the clinical development process, a Clinical Development Productivity Index was developed measuring trial success in relation to the effort invested in trials. Applying this new metric across trials in nine of the largest therapy areas showed that productivity has declined overall from 2013 to 2018 falling 27% from 2013 to 2018, heavily influenced by a decrease in productivity in Phase I of 55% over that period, and declines in Phase III since 2016. Phase II and Phase III trial productivity remained relatively stable since 2010. Declining productivity in Phase I was driven by declines in success rates of 7% and increases in trial complexity (which includes numbers of trial participants, eligibility criteria, research sites countries, and endpoints) of 6%. In 2018, complexity rose due to increases in all complexity elements excepting the number of trial sites and countries. For instance, the number of patients expected to participate in clinical trials across the nine key therapy areas increased 10% over 2017 with growth influenced by an increase of the number of patients in Phase III oncology and neurology trials.

The notable successes and failures of 2018 have also shifted our understanding of human science, disease and treatment. Since 2008 in Alzheimer's disease,

only one product received regulatory approval, while 86 other development projects were discontinued, including four in 2018. In NASH, nine new drugs were added to the late-phase pipeline as drugs with several mechanisms continue to show promise in research. There were also some notable failures in cancer, including the IDO mechanism and some with PD-1s, where other drugs had succeeded in the same tumors. However, these were offset by the large numbers of approvals and the continued flow of breakthroughs in other disease areas.

DRIVERS OF CHANGE IN CLINICAL DEVELOPMENT

Eight key trends in technology, science and data use are currently influencing clinical development. Their impact on trial design and complexity, duration and success was explored through the IQVIA Clinical Development Trends Impact Assessment completed by IQVIA therapy area experts. All trends were considered to have a high likelihood of impact, with the probability of impact ranging between 74-85%. The timing of trends is similar with all trends reaching their peak impact within 2.5-4.0 years.

Digital health and mobile technologies will enable the capture of drug efficacy and safety data remotely within the bounds of clinical trials, and are therefore expected to improve patient safety, enable virtual trial formats and ease site work burden. They will also make it easier to capture patient-reported outcomes (PRO), which are expected to shed new light on patient experience, as well as drug efficacy and safety outside the clinical setting, and lead to accelerated trial times as endpoints shift.

The emergence of new data sources and analytic tools are also changing clinical development. Curated real-world data (RWD) sources will be used to optimize trial design, speed trials by aiding selection of investigators

and sites, and enable new trial designs - e.g. by acting as virtual/synthetic control arms and supporting pragmatic, adaptive and real-world evidence (RWE) registry trial designs. On top of RWD and other big data in healthcare, predictive analytics and artificial intelligence (AI) are expected to identify new clinical hypotheses to test, minimize trial design risks and speed enrollment by identifying protocol-ready patients or by predicting which patients have disease and may be eligible for recruitment.

Shifts in the regulatory landscape were deemed the most likely to have an effect on clinical development with an 85% likelihood of impact across therapy areas. Expected to improve the likelihood of success, regulatory changes are expected to further the adoption of precision medicine approaches, enable the use of novel trial designs and endpoints and generally provide means for accelerated drug approvals.

Changes in scientific advances - shifts in drugs types being tested and biomarker test availability - are next most likely to impact clinical development and will affect greater than five therapy areas within just 2.5 years. Shifts in types of drugs being tested to disease modifying drugs, targeted therapies and Next-Generation Biotherapeutics will improve efficacy and success rates and accelerate development timelines, but will require longer-term patient follow up. The increased availability and ease of biomarker testing will allow for novel trial designs like basket trials, and help to narrow patient populations to those more likely to see effect, resulting in improvements in efficacy, safety and success.

Finally, the availability of pools of pre-screened patients and direct-to-patient recruitment are expected to facilitate trial recruitment, helping sites to hit accrual targets, decreasing trial duration and leading to accelerated market availability.

Many of the therapy areas with the most complex trials will see impacts of these trends within three years. At a therapy area level, GI/NASH, neurology and cardiovascular trials are the most likely to see rapid changes over the next several years with changes resulting from nearly all trends.

MODELING FUTURE TRIAL PRODUCTIVITY

The Clinical Development Trends Impact Assessment was also used to model the future expected impact of each key market trend on clinical development productivity across trial phases and the nine key therapeutic areas. Results show that each trend will have a differential impact on trial productivity, success and effort across therapy areas in the next five years. For example, biomarkers will have the greatest impact on clinical productivity yielding a 34% average increase across therapy areas and trial phases and the greatest increases in success rates (+27%). Similarly, pools of pre-screened patients will yield a high increase in productivity of 29% on average by driving the largest average declines in effort, at -11%.

Trends impacting productivity varied by therapy area. In oncology, pools of pre-screened patients will accelerate trial recruitment and biomarkers will improve success rates, leading to productivity improvements as high as 104% and 71%, respectively. Biomarkers will also yield consistently high improvements in productivity of over 45% across four other therapy areas: GI/NASH, rare disease, neurology and cardiovascular. In addition, oncology and neurology trials will see approximately 30% or greater improvements in productivity over the next five years – the largest increases in productivity across therapy areas – while respiratory will see the largest decrease in productivity.

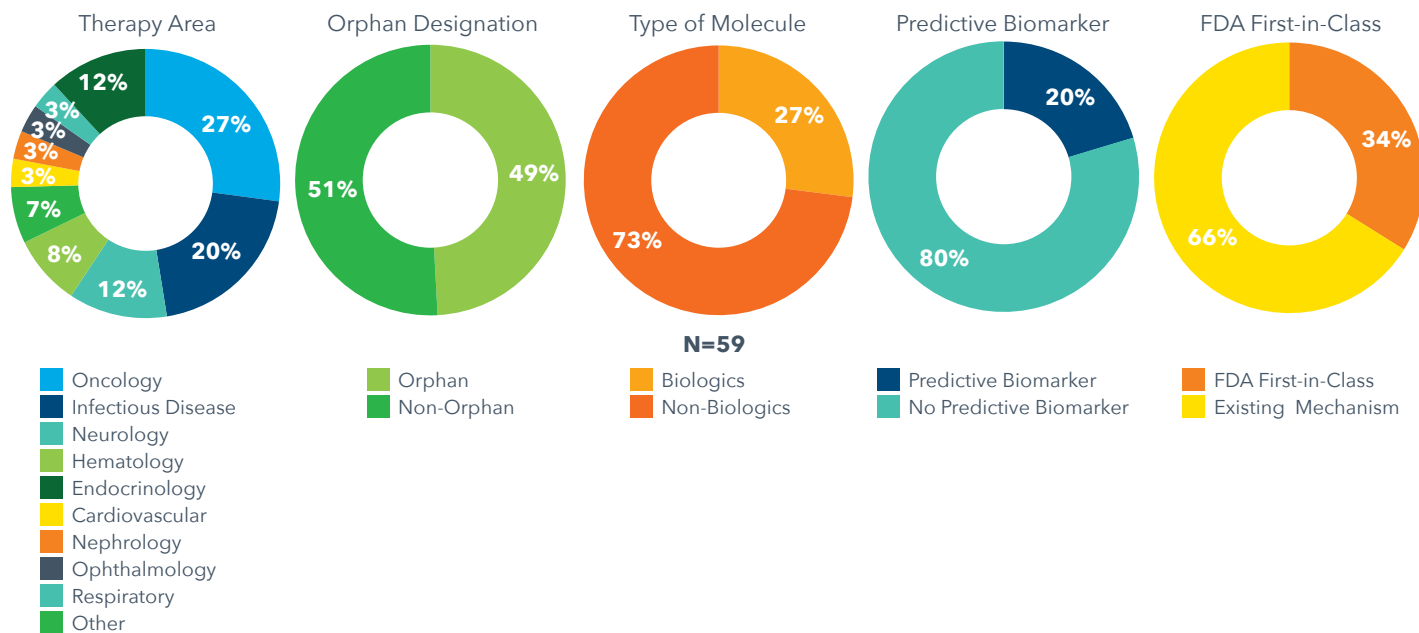
Along with biomarkers, neurology trials will see the most significant impact from regulatory changes and digital health. Respiratory trials, however, will only see positive productivity effects from RWD and predictive analytics – both derived from the growth in the use of big data and its analysis. While trends vary in their impact on productivity across phases, the most significant productivity changes will occur in Phase II trials.

New drug approvals and launches

- Fifty-nine new active substances (NAS) were launched in 2018, higher than in any of the past five years.
- Twelve of the NASs were predictive medicines that stratify patient selection based on predictive biomarkers, four were approved with a companion diagnostic and 27% were oncology medicines.
- Oncology had the most launches for a therapy area with 16 launches, including supportive care, 12 of which were orphan drugs, followed by infectious disease with 12 launches.
- Over a third of NASs launches were identified by the FDA as first-in-class, and almost half of NASs launched with an orphan drug designation for the indication at approval, demonstrating that R&D has increasingly focused on specialty, orphan and novel mechanisms.
- Of the NASs launched in 2018, 46% were approved based on data from trials with fewer than 500 subjects in total, and the average number of years that subjects collectively spend in trials cited for their approval declined.
- The development of new drugs remains a slow process, with the 2018 U.S. NASs taking a median of 13.6 years to launch from the time of their first patent filing – about two years faster than drugs launched in the prior two years.
- In 2018, four drugs were launched in less than eight years from first patent filing, including three oncology drugs and one for immune system disorders.
- In 2018, 12 drugs were launched more than 20 years after their first patent filing, reflecting in some cases older mechanisms of action being repurposed or drugs that had previously launched globally.
- Over 70% of new drugs came through the regulatory process under one of several tracks (priority review, accelerated approval, fast track or breakthrough status) intended to accelerate development and review.
- Over the past three years, those with accelerated approval designation and breakthrough status have seen shorter times from patent filing to launch than those without –15% and 19% faster, respectively.
- Of the 59 new drug launches in 2018, 38 were patented by emerging biopharma companies, and 74% of those were also registered by these companies.
- Although the importance of large pharma in originating molecules is decreasing, they remain important partners for EBP companies even as EBP are increasingly able to commercialize alone.
- Large pharma companies registered nearly half of the new drugs in 2018, approximately half of which originated with emerging biopharma companies.

A record number of innovative medicines were launched in 2018 bringing 59 new treatment options to patients

Exhibit 1: New Actives Substances (NAS) Launched for the First Time in the United States in 2018



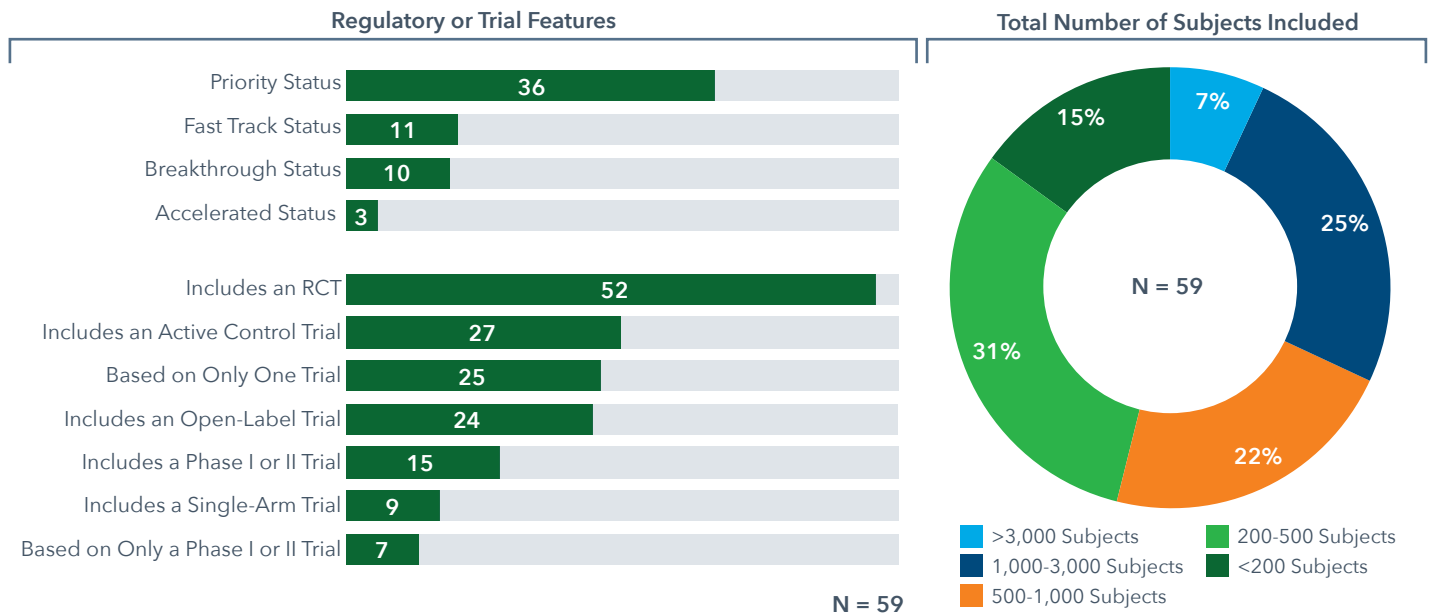
Source: IQVIA Institute, Mar 2019

- Fifty-nine NASs were launched in 2018, a higher number than in any of the past five years.
- Twelve of the NASs were predictive medicines - those medicines that stratify patient selection based on predictive biomarkers - four were approved with a companion diagnostic at time of approval and 75% were oncology medicines.
- Almost half of NASs launched with an orphan drug designation for the indication approved.
- Oncology had the most launches of any therapy area with 16 launches, 12 of which were orphan drugs, followed by infectious disease with 12 launches.
- Over a third of NAS launches were identified by the FDA as first-in-class - those drugs noted by the FDA as innovative therapies with mechanisms of action different from those of existing therapies - and 39 were specialty medicines, demonstrating that R&D has increasingly focused on specialty, orphan and novel mechanisms.
- Notable new medicines included three therapeutic nucleic acid therapies: a novel gene replacement therapy for a hereditary eye disease and the first two approved RNAi drugs for polyneuropathy in patients with hereditary transthyretin-mediated amyloidosis.
- Also notable were new classes of biologic medicines for the prevention of migraine and the treatment of certain patients with HIV-1, the first treatment for smallpox, the first oral therapy for Fabry disease and the first non-opioid therapy for the treatment of opioid withdrawal.

Chart 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 in 2018 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 therapy area includes supportive care. Other therapy area category includes: immune system disorders defined as allergy immunology and rheumatology (AIR), dermatology, gastrointestinal, genetic diseases, opioid withdrawal, and women's health. Biologics are defined by IQVIA as clearly identifiable molecules of biologic origin, including but not limited to products created with recombinant DNA technology and without necessarily adhering to classifications by regulatory bodies that are sometimes inconsistent with this approach. Percentages may not sum to 100% due to rounding. Nucleic acid therapeutics are based on nucleic acids and include but are not limited to antisense oligonucleotides, gene therapies, aptamers, microRNAs and RNAis. These drugs can be considered in cases where specific inhibition or replacement of a gene or RNA will beneficially alter protein expression.

Of the NASs launched in 2018 46% were approved based on data from trials with fewer than 500 subjects in total

Exhibit 2: Features of the Trials Cited in Approvals of NASs Launched the United States in 2018



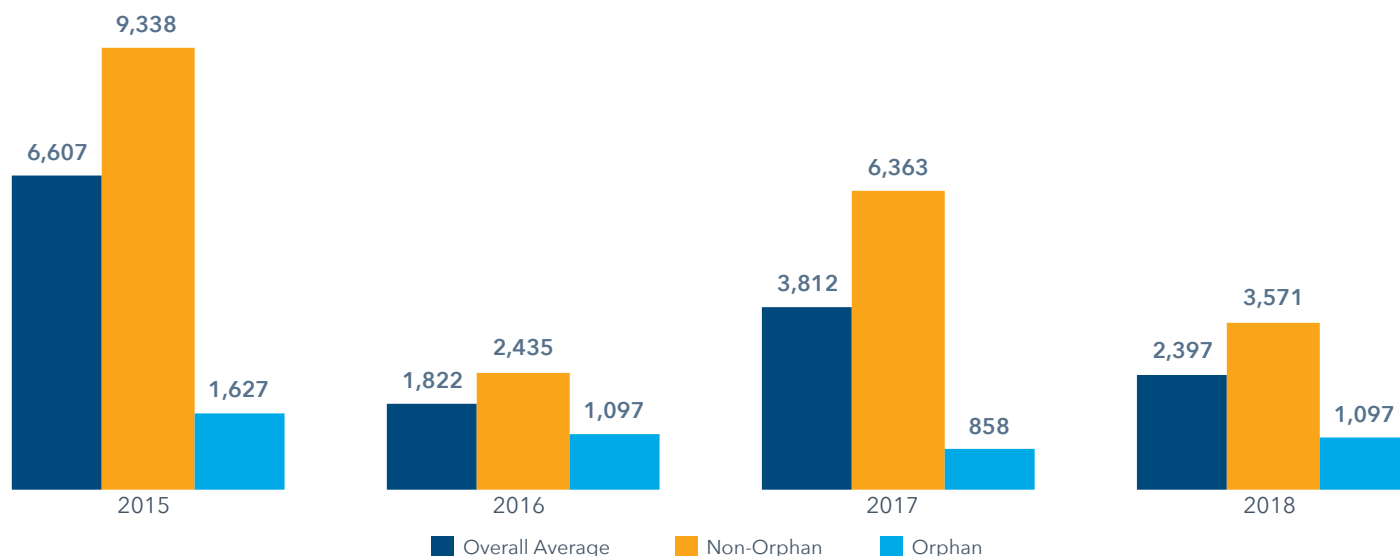
Source: IQVIA Institute, Mar 2019

- For the 2018 NASs, active control trials, open-label and cases where data from only one trial was considered, were each cited in 40–45% of NAS approvals.
- The percentage of NASs that were approved based on a regulatory package containing active control trials has increased approximately 20% since 2016, to 46%, possibly indicating a greater number of diseases now having a gold standard treatment and growing interest by payers to see comparative effectiveness data.
- Despite regulatory agencies willingness to accept novel trial designs, randomized controlled trials (RCT) continue to be the gold-standard when submitting to regulatory agencies, with the percentage of NASs including RCT in their regulatory submission packages increasing 6% since 2015.
- The number of subjects included in trials cited in FDA approvals varied widely across NAS molecules. Almost a third of 2018 NASs included more than 1,000 subjects, however, another 46% of molecules enrolled under 500.
- Fifteen percent of NAS molecules were accepted for regulatory approval with trials enrolling less than 200 participants and five of these NASs included fewer than 100 individuals. Of these, all were orphan therapies and four received regulatory approval based on only one trial.

Chart notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; NAS launches in the United States by year of launch regardless of timing of FDA approval. For regulatory trial features, analysis included trials cited in the regulatory approval announcements by the FDA as having been considered for approval; it does not include all trials associated with a molecule. Percentages may not sum to 100% due to rounding.

As more new therapies have launched, the average years that subjects collectively spend in trials cited for their approval declined

Exhibit 3: Average Number of Patient-Years Included in Trials Cited for Approval of NASs Launched in 2018



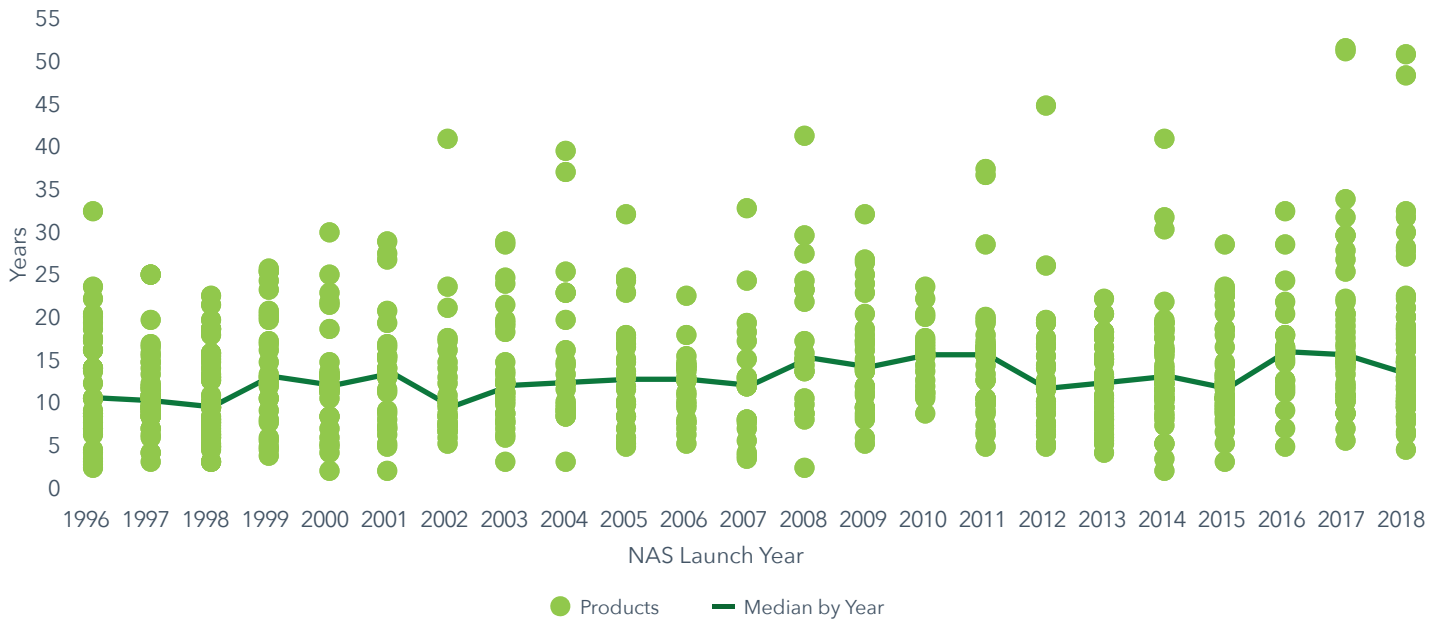
Source: IQVIA Institute, Mar 2019

- Patient-years represents the amount of time a drug has been tested in a patient population at time of approval.
- Because trial size and duration varies significantly between orphan and non-orphan drugs, non-orphan drugs are approved with a greater number of patient-years than orphan drugs.
- Orphans have been approved over the past four years with a year-average ranging from 1,554 to 3,335 patient-years of testing, with four-year average trial enrollments of 427 patients and trial durations of 7.6 years.
- Although non-orphan drugs typically treat a more diverse mix of larger treatment populations, others find niches addressing unmet needs, resulting in greater variation in patient enrollment and duration.
- Non-orphan averages in the past four years were 2,316 patients and 6.7 years, respectively.
- Over the past few years, the average number of patient-years included in trials cited for approval has been declining, as drugs types are increasingly specialty, niche and orphan drugs, which typically enroll fewer subjects and have shorter trial durations.
- The average number of patient-years for orphan NASs in 2015 were high in large part due to the approval of the non-small cell lung cancer therapy necitumumab, which included over 9,000 patient-years.
- In 2018, the drug with the lowest patient-year average was elapegademase, for the treatment of ADA-SCID. Likely due in part to the rarity and the unmet need in this space, the two regulatory trials included just 10 subjects.

Chart notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; NAS launches in the United States by year of launch regardless of 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. For each NAS, the number of subjects in each trial cited for approval was multiplied by trial duration to arrive at patient-years for that trial, and then NAS totals were calculated. Trials cited within regulatory approvals were included. Any patient-years for trials for the same molecule not cited in the regulatory approval process of the molecule were not included. ADA-SCID = adenosine deaminase severe combined immune deficiency.

New drugs launched in 2018 took a median of 13.6 years from the time of first patent filing to launch

Exhibit 4: Median Time from First Patent Filing to Launch by NAS Launch Year, United States



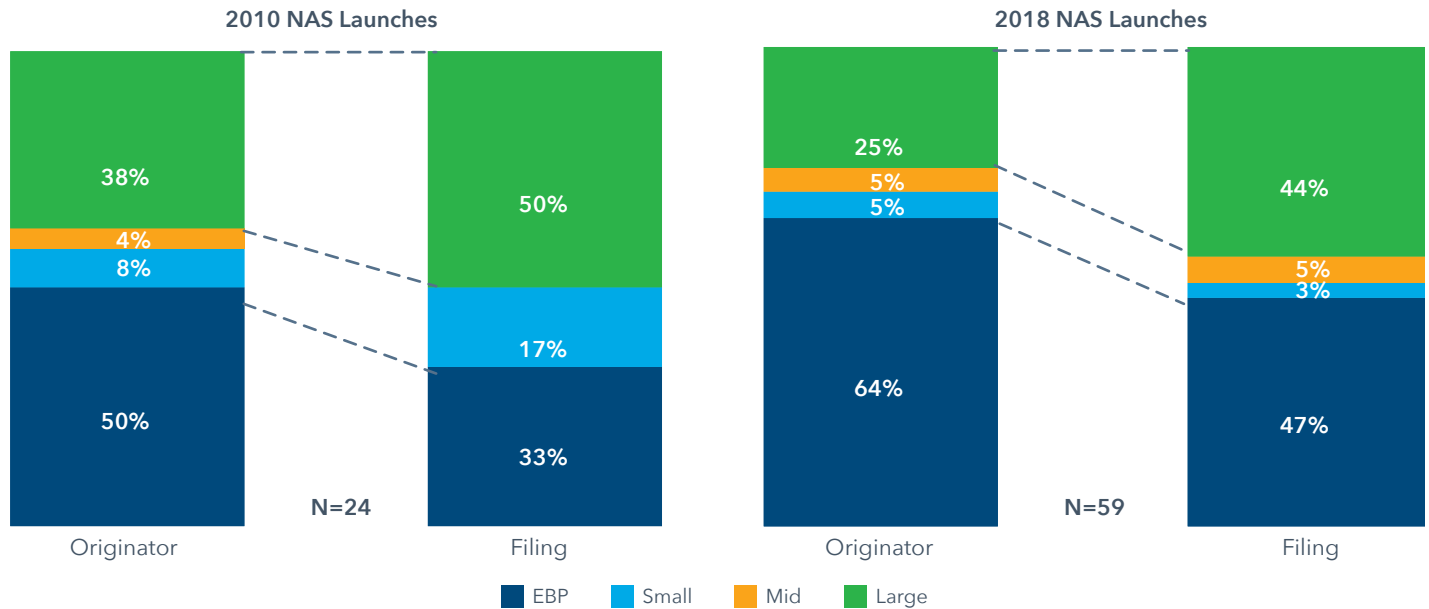
Source: IQVIA ARK Patent Intelligence, IQVIA Institute, Mar 2019

- The development of new drugs remains a slow process. In the United States in 2018, NASs took a median of 13.7 years to launch from the time of their patent filing, about two years faster than drugs launched in the prior two years, and almost 6 months faster than the median of the past five years.
- In 2018, four drugs were launched in less than eight years from first patent filing, including three oncology drugs and one for immune system disorders.
- In 2018, 12 drugs were launched more than 20 years after their first patent filing, reflecting, in some cases, older mechanisms of action being repurposed or drugs that had previously launched globally.
- Over 70% of new drugs came through the regulatory process under one of several tracks (priority review, accelerated approval, fast track or breakthrough status) intended to accelerate development and review.
- Drugs with accelerated approval averaged 14.1 years from patent to launch compared to an average of 16.2 years, 15% faster than drugs without accelerated approval among launches 2015–2018.
- Drugs with breakthrough status also showed an improvement in time from patent-to-launch, on average 19% faster than drugs without breakthrough status (an average of 14 vs.17 years, respectively).
- On average over the past four years, a slightly greater percentage of drugs fall below the median among those with accelerated approval, breakthrough status and drugs receiving approval with a single trial versus those without these attributes.

Chart notes: Compares the date of patent filing for a medicine to FDA approval for a specific indication; Some medicines have multiple indications included in the analysis.

Emerging biopharma companies patented almost two-thirds of new drugs in 2018, while large pharma patented one-quarter

Exhibit 5: Originator Companies and Companies Filing FDA Regulatory Submission by Company Segment



Source: IQVIA MIDAS restricted MAT Q4 2017; FDA websites; Clarivate Analytics Cortellis

- Large pharma companies were the filing companies for fewer than half of the 59 NAS launches in 2018.
- Emerging biopharma (EBP) companies were the originator of 38 of the NASs launched in 2018, or 64% of them.
- EBPs also filed 66% of the drugs they originated along with three obtained from other companies, thus accounting for 47% of the NASs launched in 2018.
- An increasing percentage of recent launches have originated with EBP companies, rising from 50% in 2010.
- Mid-sized and small companies originated and filed very few of the launches in 2018.
- The dynamics of development, M&A and licensing activity seem to be shifting, and emerging companies are retaining control of their assets to a greater degree.
- The importance of large pharma in originating molecules is decreasing, but they remain important partners for EBP companies even as EBP are increasingly able to commercialize alone.
- These trends also reflect a pattern of risk mitigation where co-marketed launches may remain under the control of the EBP company until they prove successful enough that the other partner acquires them. Indeed, some recent drugs that were EBP when they launched (or the EBPs themselves) were acquired by large pharma soon afterwards.
- Overall the launch environment is fragmented with 51 companies involved in the 59 launches in 2018, with Pfizer having launched four, and Lilly, Merck, Amgen, AstraZeneca and Novo Nordisk launching two each, and the remaining 45 companies with a single launch in 2018, 26 from EBP companies.

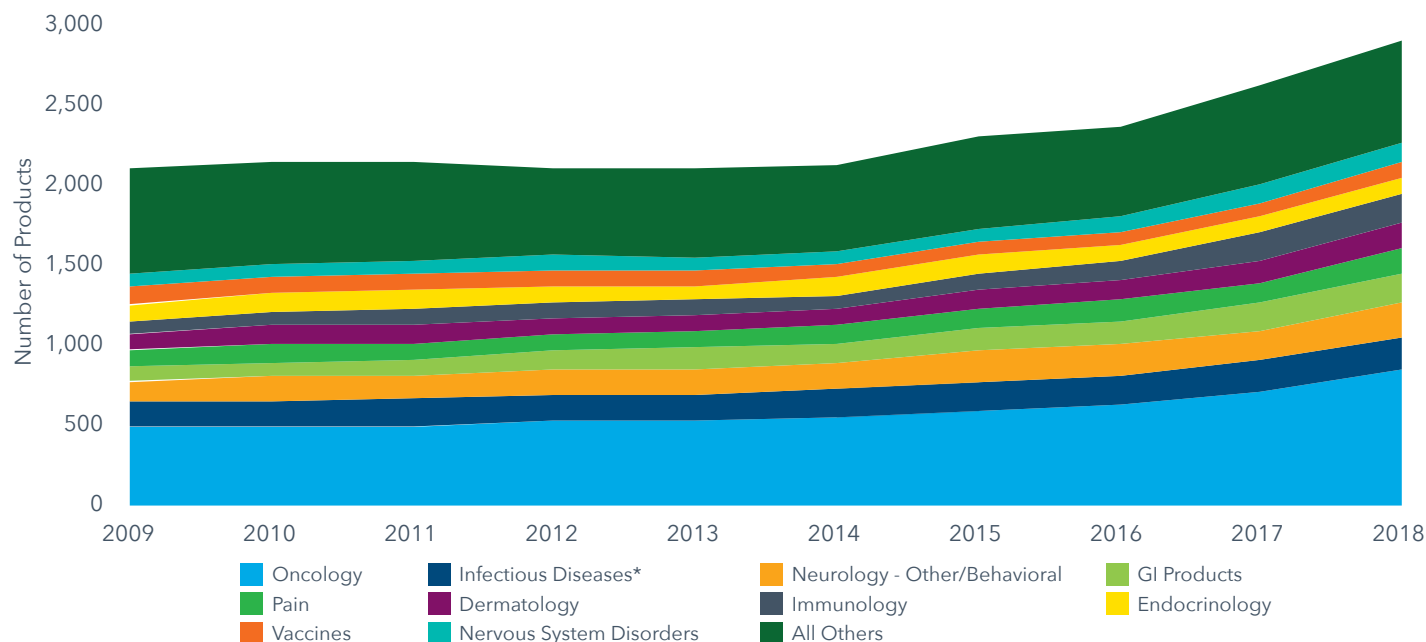
Chart notes: Originator company filed the initial patent for the product. Filing company applied for regulatory approval through the FDA. Segments defined at company level as: Large >\$10Bn; Mid \$5–10Bn; Small \$500Mn–5Bn; Emerging Biopharma (EBP) <\$500Mn OR R&D Spend <\$200Mn. Numbers may not sum to 100% due to rounding. M&A = mergers & acquisitions.

Clinical development pipeline

- The late-stage development pipeline has expanded at a steady rate over the past four years with 11% growth in both 2017 and 2018.
- Oncology drugs increased in number by 63% over the past five years, contributing over 40% of the total pipeline increase, while the number of molecules for respiratory and vaccines has declined over this period.
- Pain and dermatology drugs also increased over 50% since 2013, but each class represents just under 6% of the total pipeline.
- The total number of Next-Generation Biotherapeutics (NGB) – defined as cell, gene and nucleotide therapies – in the development pipeline reached 269 by the end of 2018, up from 120 in 2015.
- Three NGBs launched in 2018, bringing the total of NGBs available to patients to fewer than 20, reflecting the relatively recent advances and activity among these therapies.
- For NGBs, there is a significant focus on oncology as well as ophthalmology, nervous system disorders and rare diseases.
- In 2018, the overall late-phase pipeline included 2,891 drugs, up 290 from 2017. Oncology was the largest drug class with 849 pipeline products, an increase of 138 from 2017.
- ALS and other neuromuscular disorders included 23 new products under development, seven of which are in ALS and four in Huntington’s disease.
- Pipeline non-narcotic pain drugs increased by nine products in 2018 compared to 2017, as public health pressures increase around non-opioid pain management solutions.
- In 2018, emerging biopharma companies accounted for 72% of all late-stage pipeline activity, up from 61% a decade ago, while large pharma companies have seen their share drop from 31% to 20% over the same period.
- In 2018, over 1,300 life science venture capital deals were closed with an aggregate value of over \$23 billion, up from about \$10 billion in deal value in 2013.
- The 15 largest pharmaceutical companies, in aggregate, recorded more than \$100 billion for the first time in R&D expenditure across their businesses in 2018, up 32% over the past five years.

The late-stage development pipeline has expanded steadily over the past four years with 11% growth in both 2017 and 2018

Exhibit 6: Number of Late-Stage Pipeline Products by Therapeutic Drug Class, 2009–2018



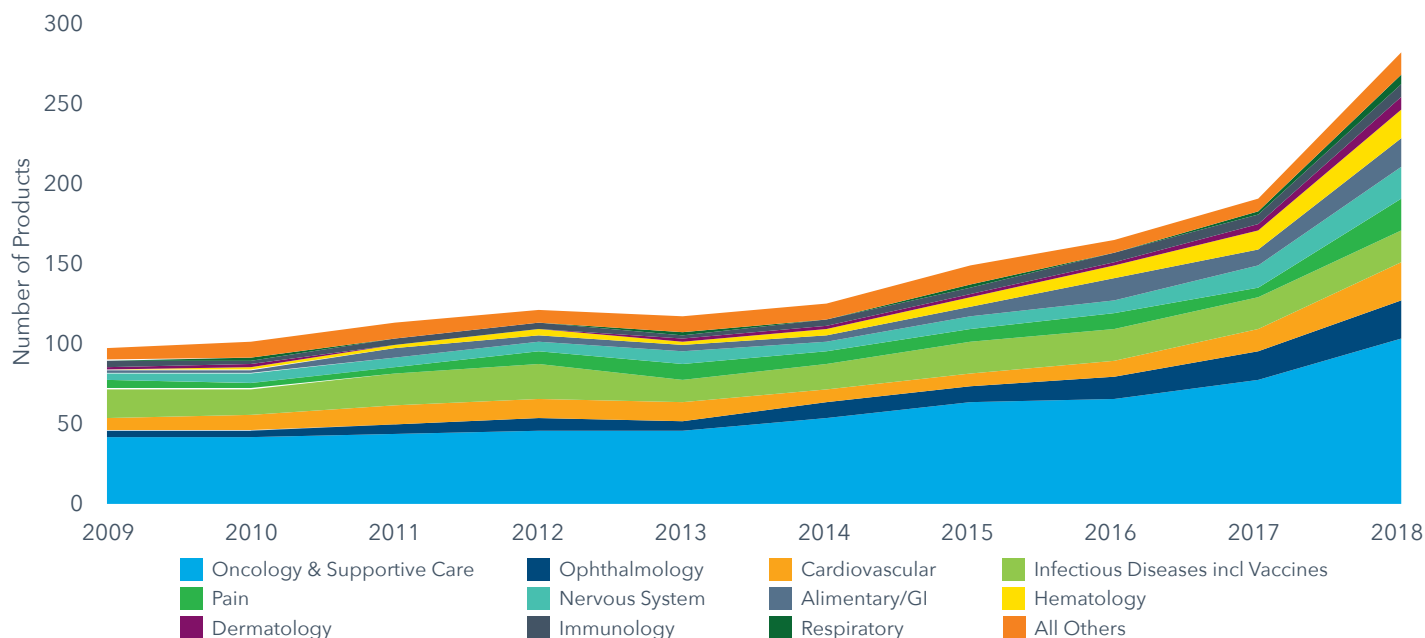
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Mar 2019

- The number of molecules in development in Phase II or later increased by 11% in 2018 to a total of 2,891 and by 39% from 2013-2018 at a CAGR of approximately 7%.
- A 63% increase in oncology products since 2013 contributed 40% of this total pipeline increase, and in 2018, oncology products now make up 29% of the pipeline.
- Neurology - other/behavioral therapies, which are for indications such as spinal muscular atrophy, cognitive disorders**, insomnia and epilepsy, make up 8% of the pipeline in 2018 and have grown 41% since 2013, with 33 new products added in 2018 alone.
- Despite product attrition between 2017 and 2018 in infectious disease, research in this area is robust, representing 7% of the late-stage pipeline and growing 12% over the past five years.
- GI therapies have grown 42% in the past five years and represent 6% of the pipeline. This growth is marked by the expansion of a robust late-stage NASH pipeline, now including 32 products, as well as products for rare diseases such as Crohn’s (12) and ulcerative colitis (19).
- Pain products in the pipeline have increased 52% from 2013-2018 and notably, 36 of these are non-narcotic, as pressures to limit and avoid opioid use have strengthened since the opioid crisis.
- The dermatology market has seen 61% growth since 2013, with 19 biotech products directed at treating psoriasis, including both specialty and traditional drugs.
- Among nervous system disorders products, 47% are potential Alzheimer’s treatments that include both specialty and traditional products, as well as small molecules and biotechnology.
- Despite decreasing numbers of vaccine products in the late-stage pipeline, vaccines continue to remain a notable portion. A 4% reduction has been realized over the past five years, with no change between 2017 and 2018.

Chart notes: CAGR = Compound annual growth rate. Late-stage pipeline is defined as active programs (activity in past three years) in Phase II through Registered. Pipeline products are categorized by their most-advanced indication, and additional indications for pipeline drugs still in earlier phases or for already marketed drugs are not counted. Infectious disease* = infectious disease products excluding vaccines; GI = Gastrointestinal; **Cognitive disorders under “neurology behavioral” drug class do not contain anti-Alzheimer’s therapies.

Next-Generation Biotherapeutics have more than doubled in number since 2015

Exhibit 7: Number of Next-Generation Biotherapeutic Pipeline Products in Late-Stage Pipeline, 2009–2018



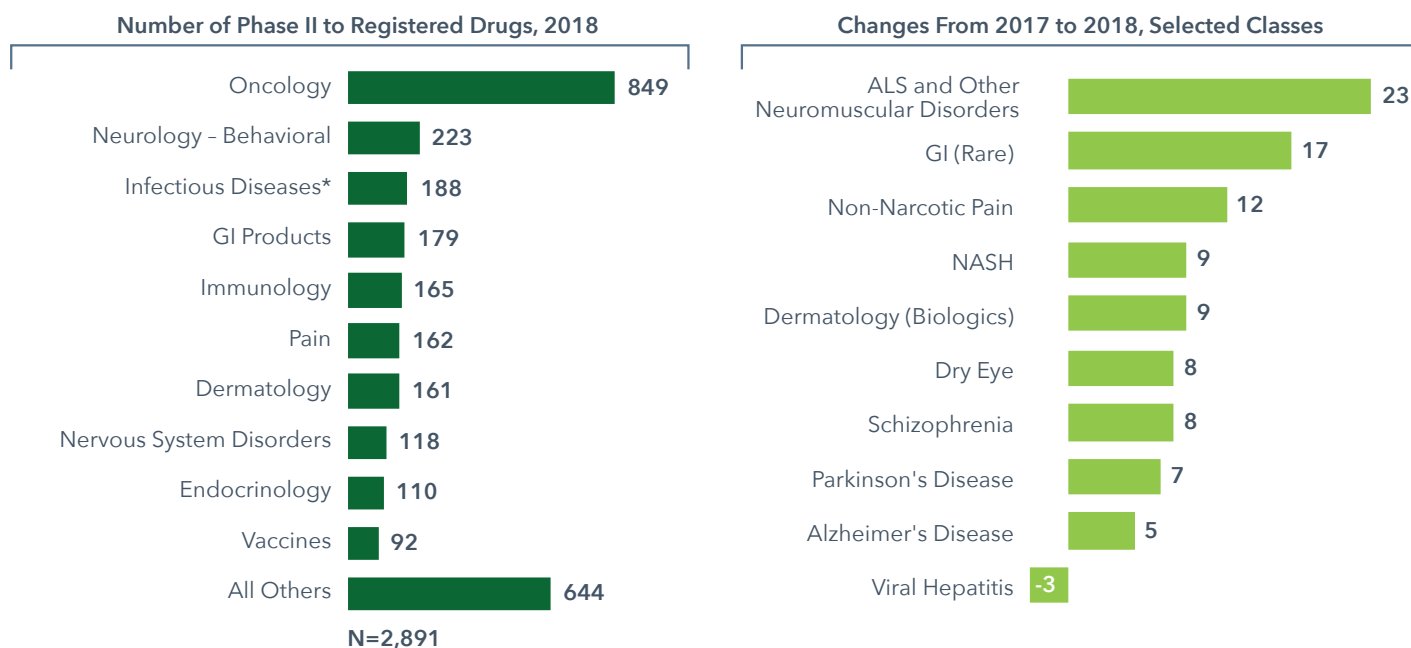
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Mar 2019

- Next-Generation Biotherapeutics (NGB) - defined as cell, gene and nucleotide therapies - make up less than 10% of the total late-stage R&D pipeline, but have more than doubled in number over the past three years as new pathways for disease treatment and cure command growing attention and investment.
- The total number of NGBs in the pipeline reached 269 by the end of 2018, up from 120 in 2015.
- Almost 80% of the late-stage NGB pipeline is in Phase II development, and the three NGBs that launched in 2018 brought the total available therapies to fewer than 20, reflecting that these are recent advances.
- In 2018, 98 NGBs in development were for oncology followed by 23 in ophthalmology, where gene therapies for retinitis pigmentosa and achromatopsia hope to build on the successful launch of voretigene neparvovec (Luxturna) for treatment of inherited retinal disease in 2018.
- Pain products include a range of gene-targeting mechanisms, like the first two successfully launched RNAi treatments to treat polyneuropathy of hereditary transthyretin-mediated amyloidosis.
- Of the 17 hematology NGBs, 13 are gene therapies, including treatments for hemophilia and thalassemia, and two are gene-editing products - one utilizing CRISPR-Cas9 technology for the treatment of thalassemia and sickle cell anemia.
- Treatments for nervous system disorders like MS, Parkinson’s, ALS, Alzheimer’s and other neuromuscular disorders account for 18 NGB treatments, up from just five in 2009. Gene therapies are also under investigation for Parkinson’s disease, Alzheimer’s disease and spinal muscular atrophy.

Chart notes: Late-stage pipeline is defined as active programs (activity in past three years) in Phase II through Registered. Next-Generation Biotherapeutics defined as cell and gene therapies or nucleotide therapies with mechanisms including: cell therapy, dendritic cell therapy, NK cell therapy, T-cell therapy, CAR-T cell therapy, T-cell receptor therapy, stem cell therapy, bacterial cell therapy, CIK cell therapy, CIK-CAR therapy, whole cell vaccine, dendritic cell vaccine, bacterial cell vaccine, DNA vaccine, RNA vaccine, exon skipping, nucleic acid-based, gene therapy, oligonucleotide, antisense, RNAi, microRNA mimic, gene editing, CRISPR-Cas9, zinc finger nuclease, RNA therapy, and mRNA therapy.

Late-stage pipeline growth is mostly driven by specialty and niche therapies across a range of diseases

Exhibit 8: Late-Stage Pipeline Products and Changes from 2017 in Selected Classes



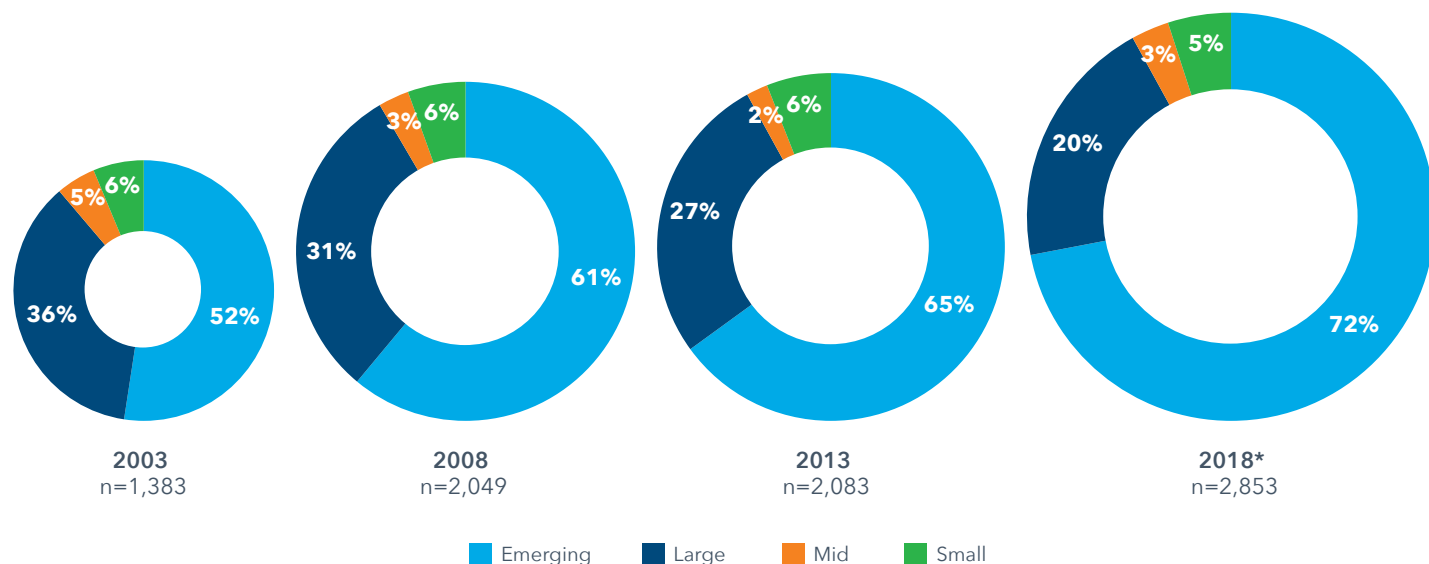
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Mar 2019

- Oncology represents the largest drug class with 849 of the 2,891 pipeline products, up by 138 in 2018.
- The neurology pipeline focuses on behavioral health, including depression, psychoses, ADHD and substance abuse and dependency treatments. Along with the robust pain pipeline these reflect a response to the opioid crisis.
- The infectious disease pipeline has fewer drugs in development than 2017, despite continuing need for novel antibiotics and antivirals.
- GI products in the pipeline include standard classes, such as anti-ulcerants, as well as rare and orphan specialty drugs, with continued growth, as among non-alcoholic steatohepatitis (NASH) products.
- In 2018, 18% of the GI products were NASH related, up from 14% in 2017. As there is no standard of care in NASH, the pipeline reflects efforts to serve an unmet need, and potential treatments include specialty medicines, stem cell therapies and RNAi therapies.
- The ALS and Other Musculoskeletal drug class has 23 new products, seven of which are in ALS and four in Huntington’s disease.
- Non-narcotic pain drugs grew by nine products in 2018, as public health pressures increase around non-opioid pain management solutions.
- The dermatology pipeline is becoming increasingly focused on specialty products, with 14 biologics in 2018 up from seven in 2017, and the entry of biosimilars into the pipeline.
- Viral hepatitis has seen a decrease in pipeline activity, and recent marketed products have contributed to this decline.

Chart notes: Late-stage pipeline is defined as active programs (activity in past three years) in Phase II through Registered. Pipeline products are categorized by their most-advanced indication, and additional indications for pipeline drugs still in earlier phases or for already marketed drugs are not counted. Infectious disease* = infectious disease products excluding vaccines; ALS = amyotrophic lateral sclerosis; GI = gastrointestinal; ADHD = attention-deficit/hyperactivity disorder.

Emerging biopharma companies now account for over 70% of the total R&D pipeline

Exhibit 9: Percent of Late-Stage Pipeline by Company Segment



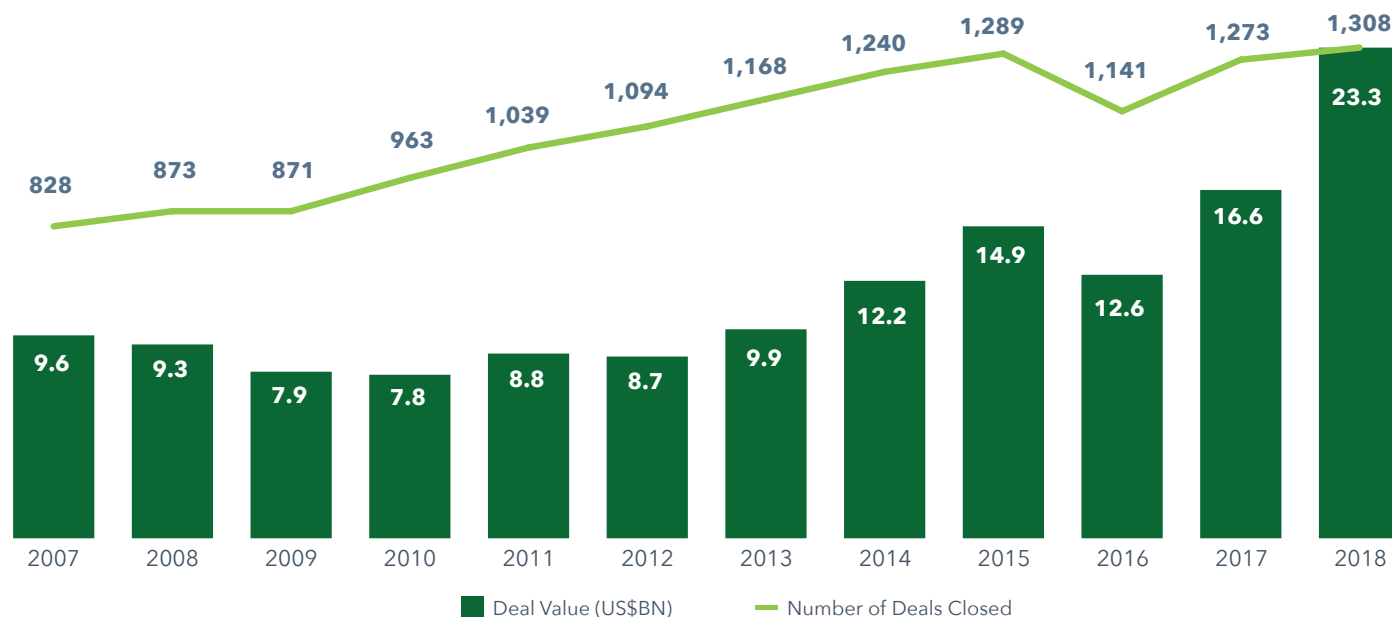
Source: IQVIA Pipeline Intelligence, Apr 2018; IQVIA Institute, Mar 2019

- Emerging biopharma companies (EBP) are defined as companies that are estimated to spend less than \$200 million annually on R&D and have less than \$500 million in revenue.
- EBP companies accounted for 72% of the total R&D pipeline in 2018, compared with 61% in 2008.
- Large pharma companies – those with more than \$10 billion in annual pharmaceutical sales – have seen their share drop from 31% to 20% over the same period.
- EBP growth is being driven by smaller EBP companies being the most active in the fastest growing areas of oncology and orphan drugs, and having a diminishing need to partner or be acquired to develop their innovative medicines.
- Although the majority of the assets of EBPs used to be sold or licensed before the launch of a novel product, 47% of therapies were launched in the United States in 2018 were by EBP companies.
- Since 2013, the absolute number of active R&D compounds has increased 37%, and this will likely support a continued increase in the number of EBP-launched drugs over the next five years.

Chart notes: *Reflects pipeline through Oct 4, 2018. Companies assigned to segments based on MAT Sep 2018 Revenues or 2017 R&D Spend. Segments defined at company level as: Large >\$10Bn; Mid \$5–10Bn; Small \$500Mn–5Bn; Emerging Biopharma (EBP) <\$500Mn OR R&D Spend <\$200Mn. If multiple companies involved in a project, the larger segment takes precedence. Percentages may not sum to 100% due to rounding.

U.S. venture capital activity in life sciences has been rising in absolute terms and the number of deals

Exhibit 10: U.S. Venture Capital Deal Value in US\$Bn and Number of Deals Closed



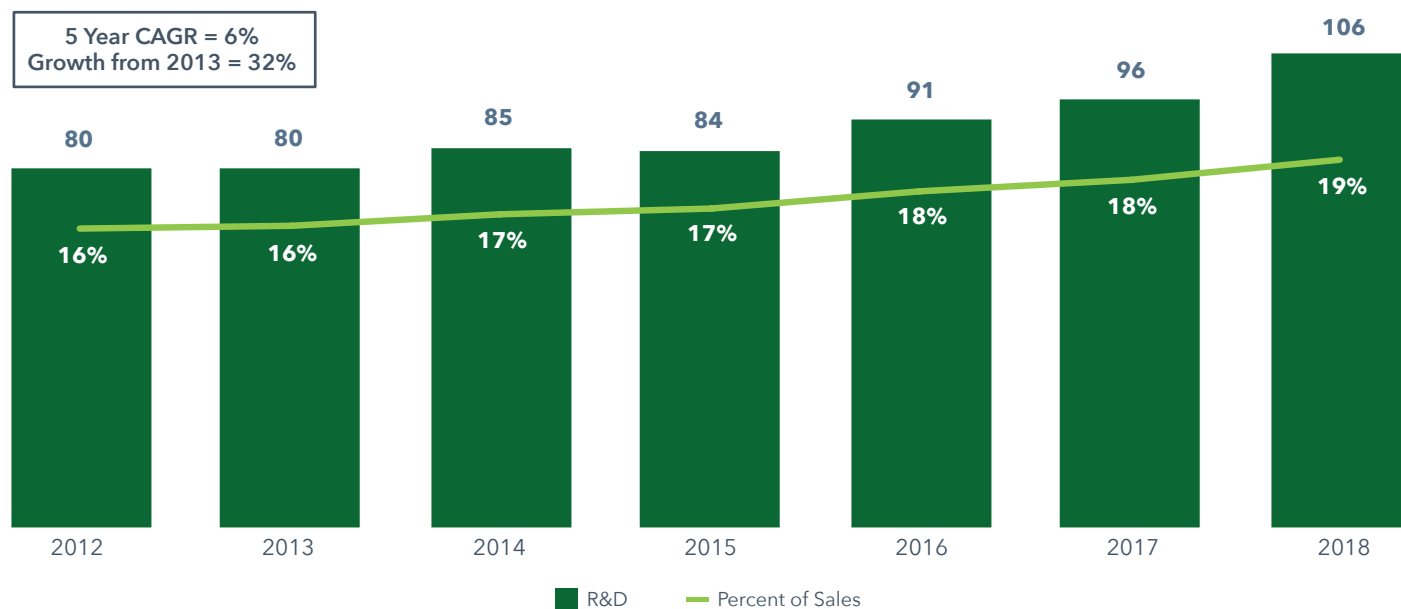
Source: National Venture Capital Association. Accessed Dec 2018. Available from: <https://nvca.org/research/research-resources/>

- In 2018, 1,308 life science venture capital deals were closed with an overall value of over \$23 billion.
- Life science venture capital deal values have grown sharply in the past five years, with a five-year CAGR of 19%.
- Venture capital deals have been rising steadily since 2007, following a dip in 2016 in venture capital investment, in part due to uncertainties around the U.S. election.¹
- Despite a drop in 2016, the number of deals have rebounded since then and are up 15% - now higher than any other year - while the corresponding deal value nearly doubled from 2016.
- Growth in 2018 was in part due to a strong run on public markets, including seven of the 10 largest IPOs in Q4 coming from the healthcare sector.²

Chart notes: CAGR = Compound annual growth rate.

Large pharma R&D spending exceeded \$100 billion for the first time in 2018, up more than 30% over the past five years

Exhibit 11: Large Pharma R&D Spending and Percentage of Sales, US\$BN



Source: Data taken from company financial statements; IQVIA Institute, Mar 2019

- The 15 largest pharmaceutical companies in aggregate recorded more than \$100 billion for the first time in research and development expenditure across their businesses in 2018, up 32% over the past five years.
- Total spending reported by large pharma companies has increased substantially from 2013–2018, with a five-year CAGR of 6%.
- The R&D percentage of sales by large pharma companies has increased over the same period; in 2018, 19% of total sales was on R&D, up from 16% in 2013.
- These investments in medical innovation are being made across a more diverse range of disease areas, mechanisms, and companies.
- 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.

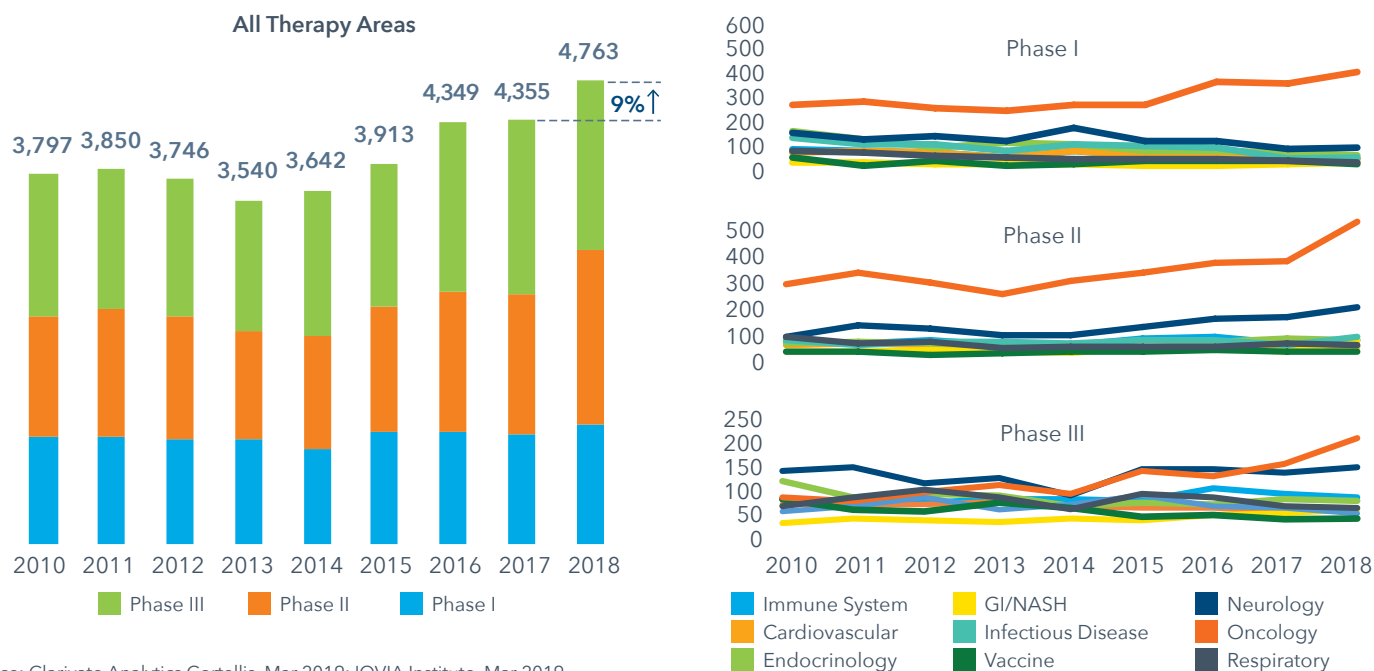
Chart notes: CAGR = Compound annual growth rate. R&D as a percent of sales includes COGS, SGA, R&D and operating margin (OM). Companies include: Pfizer, Merck, Novartis, Sanofi, AstraZeneca, GlaxoSmithKline, Roche, Johnson & Johnson, Abbvie, Eli Lilly, Teva, Bristol Myers Squibb, Amgen, Novo Nordisk and Gilead.

Clinical trial activity metrics and notable breakthroughs

- The number of clinical trials started in 2018 was 4,768, reflecting an increase of 9% over the prior year and growth of 35% over the past five years.
- The greatest increase in the number of trials occurred in Phase II, which has increased 26% over the prior year and is up 61% since 2013.
- The number of clinical trials in GI/NASH and oncology have increased significantly in 2018, up 42% and 27%, respectively, while trial activity in the other major therapy areas, including endocrinology and respiratory, declined.
- For those drugs that successfully progress from Phase I to the end of development, overall progression time has increased.
- Overall progression time rose by an aggregate of six months across all development stages in 2018 to reach an average of 12.5 years from the initiation of Phase I clinical development to registration of a drug.
- The composite success rate of clinical development stages from Phase I trials to regulatory submission fell to 11.4% in 2018, down from 14.4% in 2017 and below the average of 14% in the prior ten years.
- Both Phase I and Phase III trials saw declines in success rates in 2018 of 7.5% while Phase II improved by less than 1%.
- Composite success rates vary by therapy area in 2018 between 6–15%, with rates for rare diseases and GI/NASH exceeding averages.
- To examine the productivity of the clinical development process, a Clinical Development Productivity Index is useful to measure trial success in relation to the effort invested in trials.
- Trial productivity has been highest for respiratory, infectious disease and endocrinology and lowest for oncology.
- Productivity declined 27% from 2013 to 2018 across all trial phases, heavily influenced by a decrease in productivity in Phase I.
- Phase I trials showed the greatest increase in complexity, with a 6% increase over 2017 and 35% increase since 2013, particularly in oncology and immune system diseases, but this growth is tempered by declines in other therapy areas, such as vaccine trials.
- In Phase III trials, complexity in GI/NASH trials has increased notably, while complexity in oncology is being driven by increases in endpoints and eligibility criteria, offset by declines in the number of countries for sites.
- A number of notable breakthroughs occurred in 2018, some based on success and others based on failure, but collectively contributing to the advancement of understanding human science, disease and treatment.

The number of clinical trials initiated in 2018 is up 9% over 2017, due partly to an increase in Phase II oncology trials

Exhibit 12: Number of Clinical Trials in All Therapy Areas and Select Therapy Areas by Phase



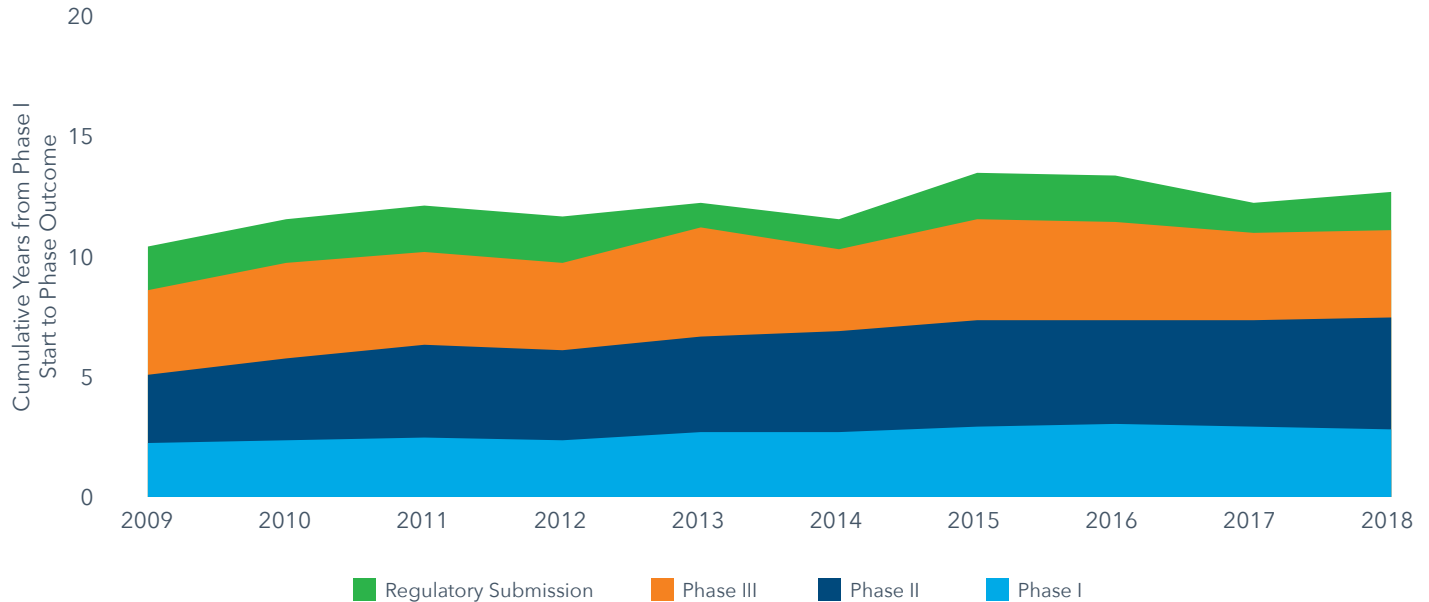
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- The total number of clinical trials started in 2018 was 4,768, reflecting an increase of 9% over the prior year and growth of 35% over the level five years ago.
- Clinical trials across all phases in GI/NASH and oncology have increased significantly in 2018, up 42% and 27%, respectively, while trial activity in the other major therapy areas, such as endocrinology and respiratory, declined.
- The total number of Phase I and Phase III trials has remained relatively flat since 2016, with growth in oncology trials offsetting declines in other therapy areas.
- Phase II trials, in comparison, increased 26% over the prior year and are up 61% since 2013.
- The trend in Phase II trials has been mostly driven by oncology, although there are also a growing number of neurology and hematology* trials.
- The number of rare disease trials increased 21% from 2017 to 2018, reflecting an active trend towards the development of rare disease medicines.

Chart notes: Average reported is the mean. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. 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. Therapy areas included were: oncology, immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine, neurology and respiratory. Vaccine trials are infectious disease only. Totals for 2018 may be reflecting delayed filing of those trials into trial databases. *Hematology trials not shown.

The cumulative time from beginning of Phase I trials to the end of development has increased over the past ten years

Exhibit 13: Average Cumulative Phase Durations from Phase I Start to Phase Outcome



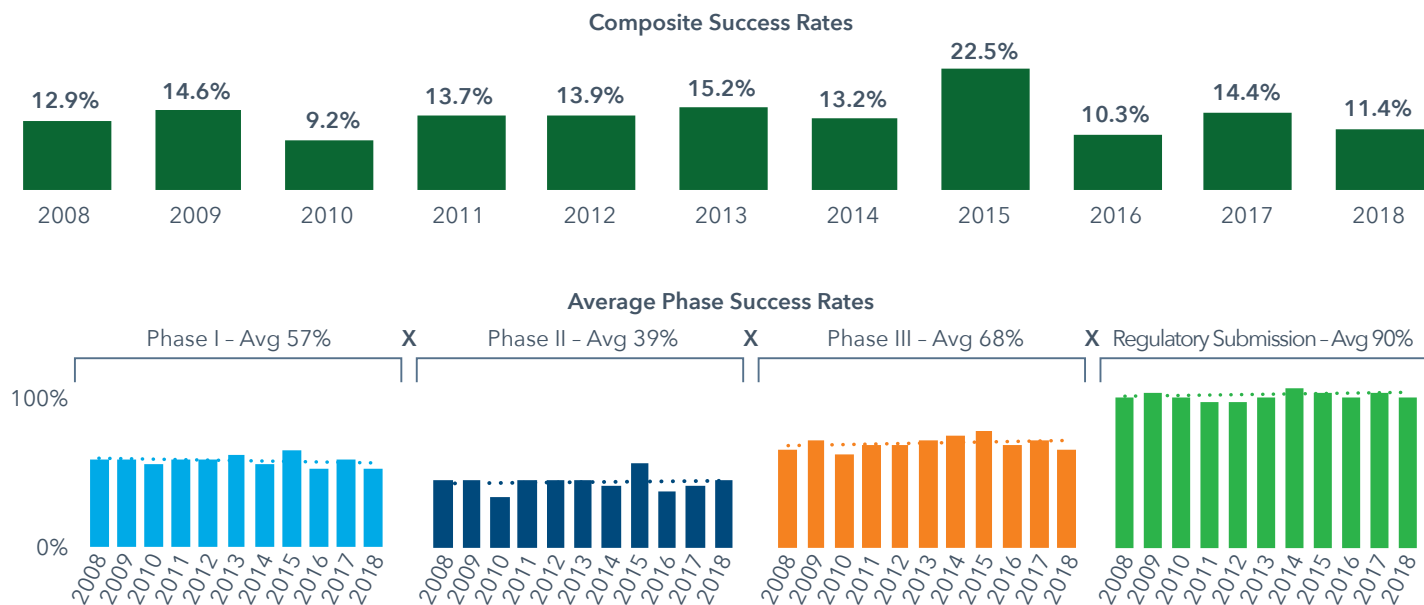
Source: IQVIA Pipeline Intelligence, Mar 2019; IQVIA Institute, Mar 2019

- The composite progression time for all drugs across all development stages - the time from the start of human trials (Phase I) to the regulatory decision (either successful or not) to enable marketing - has been rising over the past decade.
- Overall progression time reached 12.5 years in 2018, up six months over the 2017 combined average, and resuming the gradual lengthening of progression time for all drugs in development.
- Overall, the total time from Phase I to regulatory decision, regardless of product failure or success, has increased 26% since 2010.
- In oncology, successful products have dipped below the ten-year average of 12.6 years, to 11.6 years in 2018, after 2–3 years of slower progressions. Oncology products have particularly benefited from faster regulatory reviews, with the time from submission to approval dropping to about a year over the past three years.
- Successful rare disease drugs have an average 12.2 years of progression time to regulatory approval over the past ten years. The regulatory approval timeframe has decreased, as rare disease drugs have benefited from a range of novel approval pathways and review mechanisms.

Chart notes: Phase duration is calculated from start and start of subsequent Phase or the date of a decision to discontinue, suspend or withdraw research programs. End is also based on drugs being inactive for more than three years and they are assigned as inactive in the year the 3 years of inactivity occurs, while duration is calculated based on the point three years prior when the activity ceased. Average duration in months is reported as the mean. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Each phase’s duration is based on products that finished that year and are mutually exclusive. For failed records and overall, each phase is based on having prior phase success.

The composite success rate of clinical development stages from Phase I trials to regulatory submission fell to 11.4% in 2018

Exhibit 14: R&D Composite Success Rate and Average Phase Success Rates Phase I to Filing, 2008–2018



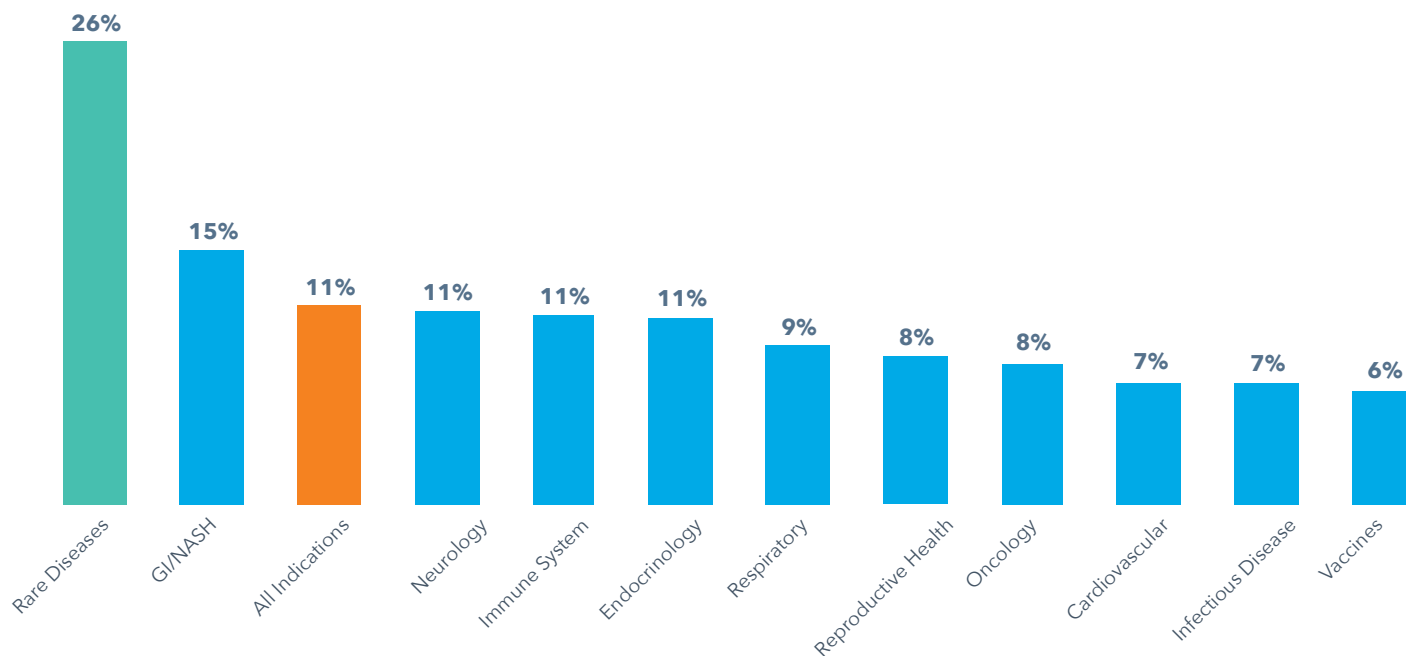
Source: IQVIA Pipeline Intelligence, Mar 2019; IQVIA Institute, Mar 2019

- The composite success rate of clinical development stages from Phase I trials to regulatory submission fell to 11.4% in 2018, down from 14.4% in 2017.
- Composite success rates fluctuated over the past decade, with 2015 an exceptional year where the rate exceeded 22%.
- The composite success rate for 2018 was also well below the average of 14% for the prior ten years (2008–2017) in part due to drops in success of Phase III and Phase I trials.
- The success rates for Phase I and Phase III trials both fell by about 7.5% while Phase II improved by less than 1%.
- The mix of drug types under development and the number of drugs per therapy area changed during the past decade – shifting toward oncology, biologic and specialty drugs – where the success rates for oncology is slightly lower than for research overall.
- In the years from 2009–2018 the composite success rate for oncology products averaged 12.0% compared to 14.1% for all other products.

Chart notes: Composite Success Rate = Phase I x Phase II x Phase III x Regulatory Submission. See methodology for full method of success calculations.

Composite success rates vary by therapy area between 6-15% in 2018, with rates for rare diseases and GI/NASH exceeding averages

Exhibit 15: R&D Composite Success Rate in 2018 by Therapy Area



Source: IQVIA Pipeline Intelligence, Mar 2019; IQVIA Institute, Mar 2019

- GI/NASH is the only therapy area to have success rates above the average; this therapy area includes a wide range of indications with recent approvals including traveler’s diarrhea, chronic idiopathic constipation, ulcerative colitis and Crohn’s disease.
- Neurology showed a composite success rate of 11%. A number of notable neurology products were approved in 2018, including three new biologic products for migraine, drugs for rare neurological diseases such as Lennox-Gastaut syndrome, Dravet syndrome and hereditary transthyretin-mediated amyloidosis.
- Vaccines in infectious disease had the lowest composite success rate at 6%, in part due to specific challenges including the high cost of development, patient recruitment and retention, and limited understanding how to trigger immune response to deliver disease-specific protection.
- Despite the accounting for almost 30% of the R&D product pipeline in 2018, composite success rates for oncology are only 8%, in part due to trial complexity as well as Phase II proof of concept/dosing trials imperfectly promoting candidates to Phase III.

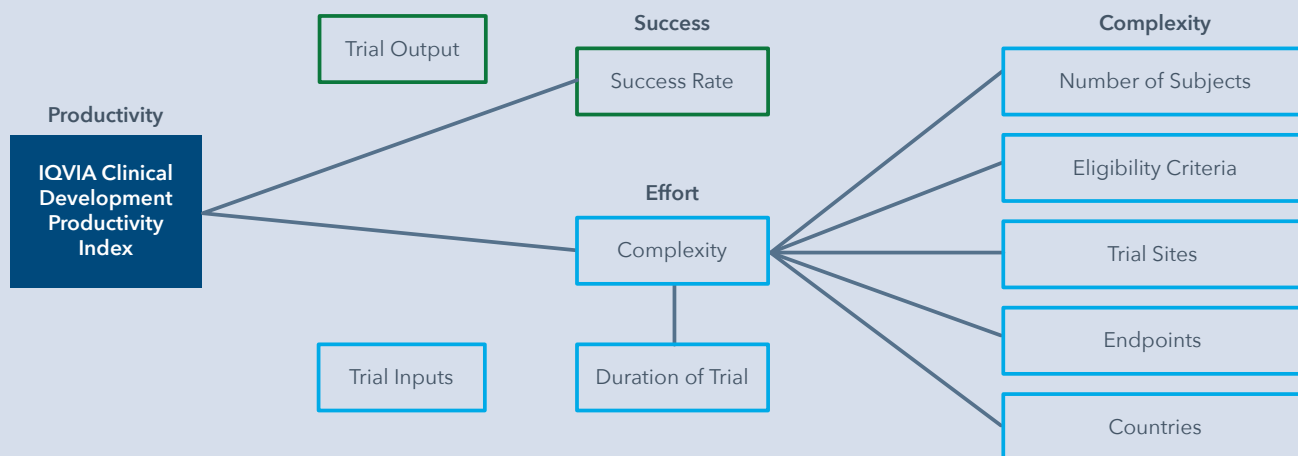
Chart notes: See methodology for full method of success calculations. Vaccine trials were infectious disease only. Rare disease category represents rare diseases across therapy areas and as such cannot be added to other therapy areas.

A Clinical Development Productivity Index

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 (see Exhibit 16).

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.

Exhibit 16: Clinical Development Productivity Index



Source: IQVIA Institute, Apr 2019

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 Clarivate Analytics Cortellis clinical trial database, and success metrics were calculated from IQVIA™ Pipeline Intelligence (see Methodology).

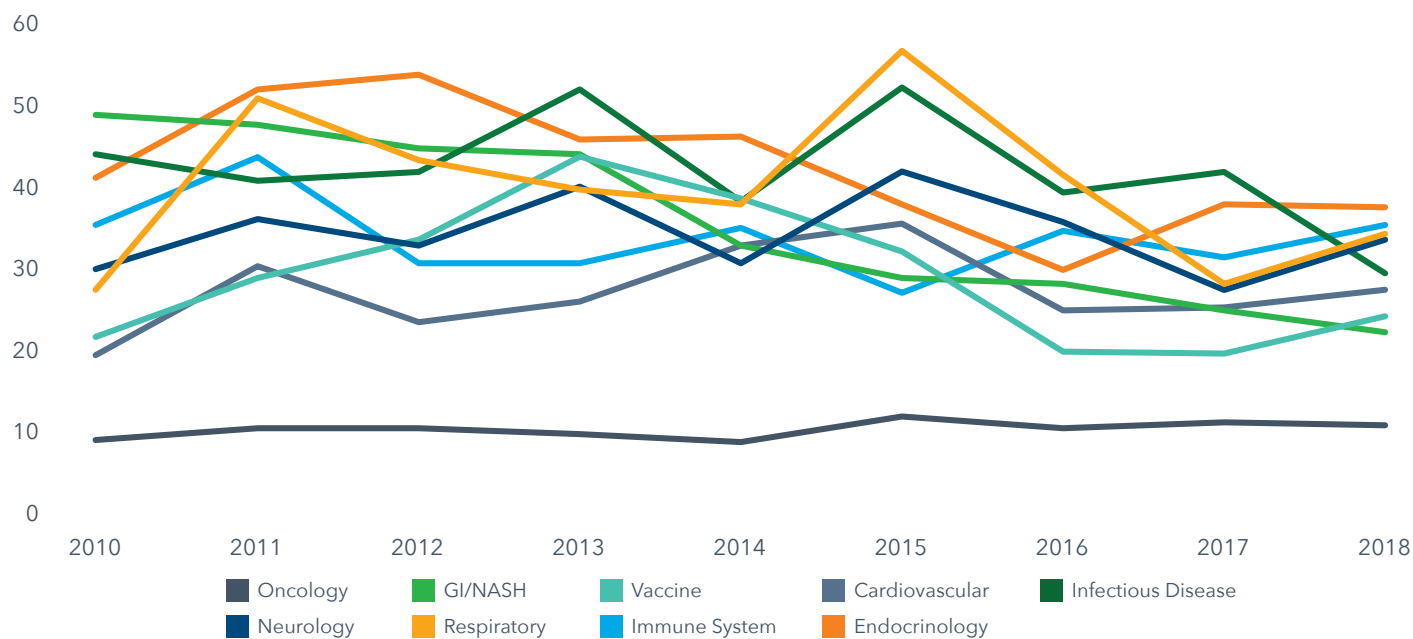
An analysis of productivity was conducted across nine key therapy areas: oncology, immune system, GI/NASH, endocrinology, respiratory, vaccine, infectious disease, neurology and cardiovascular, with the rare diseases that fall within these categories noted separately.

A factor of 97.61 was placed in the numerator of the productivity index formula (see below) and multiplied with success to allow historical (2010–2018) productivity values to stretch between a min of 0 and max of 100.

$$Productivity = \frac{Success \times factor}{(endpoints \times eligibility\ criteria \times sites \times patients \times countries) \times trial\ duration}$$

Trial productivity has been highest for respiratory, infectious disease and endocrinology trials and lowest for oncology

Exhibit 17: Trial Productivity Across All Phases by Therapy Area, 2010–2018



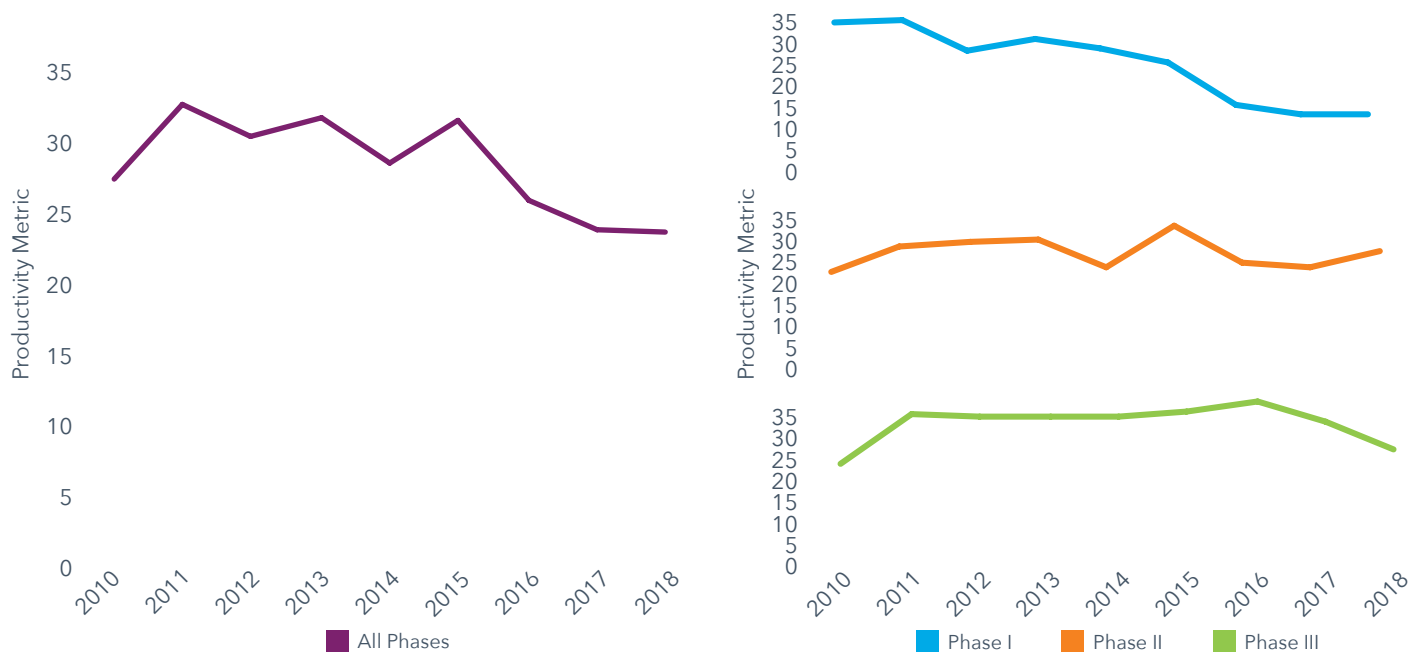
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Among therapy areas across all phases, oncology has the lowest productivity and has shown only a modest CAGR of 2% since 2010.
- Conversely, cardiovascular disease has seen a substantial increase in productivity, climbing 41% since 2010 with a CAGR of 4% through 2018.
- A number of therapy areas have seen drops in productivity, in particular infectious disease, respiratory, neurology, GI/NASH and endocrinology with GI/NASH showing the greatest drop at a loss of 55% since 2010 followed by infectious disease at a loss of 33%.
- When viewed across all phases of development, Immune system in among the therapy areas that has seen the least amount of change in productivity since 2010, likely due to stability in both complexity and success rates over the past eight years.
- When considered since 2011, productivity in respiratory has dropped significantly by over 30%.

Chart 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 III/III and III. Data shown is a weighted average. Vaccine trials restricted to infectious disease vaccines only.

Productivity declined 27% from 2013 to 2018 across all trial phases, heavily influenced by a decrease in productivity in Phase I

Exhibit 18: Trial Productivity, 2010–2018



Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Productivity has declined over 50% in Phase I since 2010 but remains stable in Phase II and III, due in part to stable complexity levels in these Phases.
- Phase I productivity fell 54% from 2010 to 2016, but slowed between 2016 to 2018 dropping only 13%.
- Phase I productivity is heavily influenced by trends in trial complexity, which has risen 35% since 2013. Trial duration during this time only increased 5% and success remained flat.
- Declines in Phase I are due to drops in productivity across infectious disease, immune, respiratory, neurology, GI/NASH and endocrinology.
- Productivity in Phase I in oncology and vaccine remained stable, while there was an increase in cardiovascular trials.
- Productivity in Phase II and Phase III is relatively flat, although there is a slight rise in Phase III, mirroring similar trends in complexity, success and trial duration.
- In Phase II, oncology trials have had relatively stable productivity from 2010–2018, while cardiology productivity increased 5% from 2013–2017.
- Phase III trials in oncology had an average productivity of 8.4 from 2010–2013, growing 24% in 2018 to 10.5.

Chart 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. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Data shown is weighted average. All TAs = All therapy areas: oncology, immune system, GI/NASH, endocrinology, respiratory, vaccine, infectious disease, neurology and cardiovascular.

Success rates have declined in Phase I driven by declines in oncology, immune system, GI/NASH, infectious disease and respiratory trial success

Exhibit 19: Trial Success Rates by Phase, 2010-2018



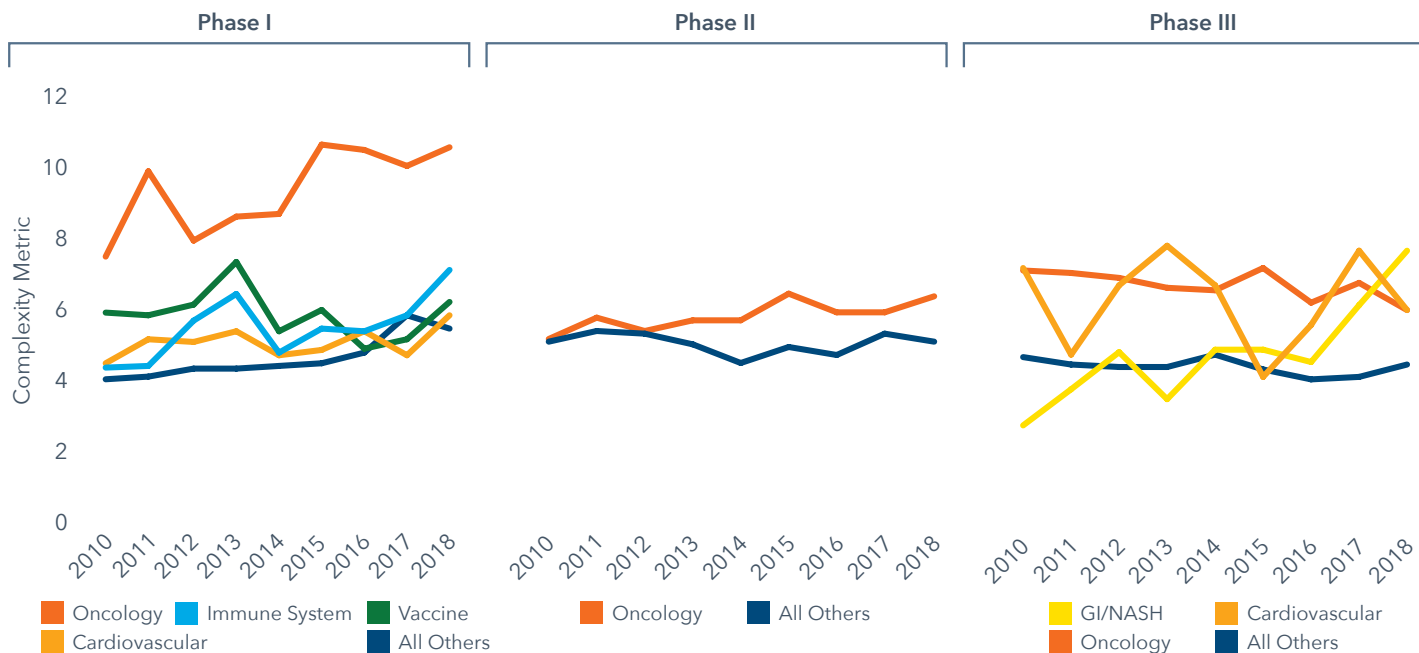
Source: IQVIA Pipeline Intelligence, Mar 2019; IQVIA Institute, Mar 2019

- Phase I success rates have declined 7% since 2010, influenced by oncology, immune system, endocrinology, GI/NASH, infectious disease and respiratory products.
- Success rates for Phase I for neurology, vaccine and cardiovascular products have not changed significantly since 2010.
- Phase II success rates have been stable since 2010, with most therapy areas remaining flat or declining slightly. Of note, GI/NASH has declined in this phase, from a high of 67% in 2012 to 35% in 2018, while the success of cardiovascular products have increased slightly from 22% in 2010 to 44% in 2018.
- In 2018, Phase III success rates ranged from 38% for cardiovascular products to 89% for immune system products.
- Phase III trial success has been growing at a CAGR of 5% from 2010 to 2017, however, 2018 has shown a drop of over 15% from the previous year, due to the downward pressure from failed cardiovascular and infectious disease products.
- The low Phase III success rate in 2010 for Phase III is in part due to few respiratory product successes in this year, and the low Phase II success rate in 2010 is influenced by respiratory and neurology products (with 13% and 15% success, respectively in that year).

Chart notes: See methodology for full method of success calculations. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Data shown is weighted average. All TAs = All therapy areas: oncology, immune system, GI/NASH, endocrinology, respiratory, vaccine, infectious disease, neurology and cardiovascular.

Complexity for Phase II and Phase III studies has not changed significantly since 2010 for most therapy areas

Exhibit 20: Trial Complexity by Phase and Therapy Area, 2010–2018



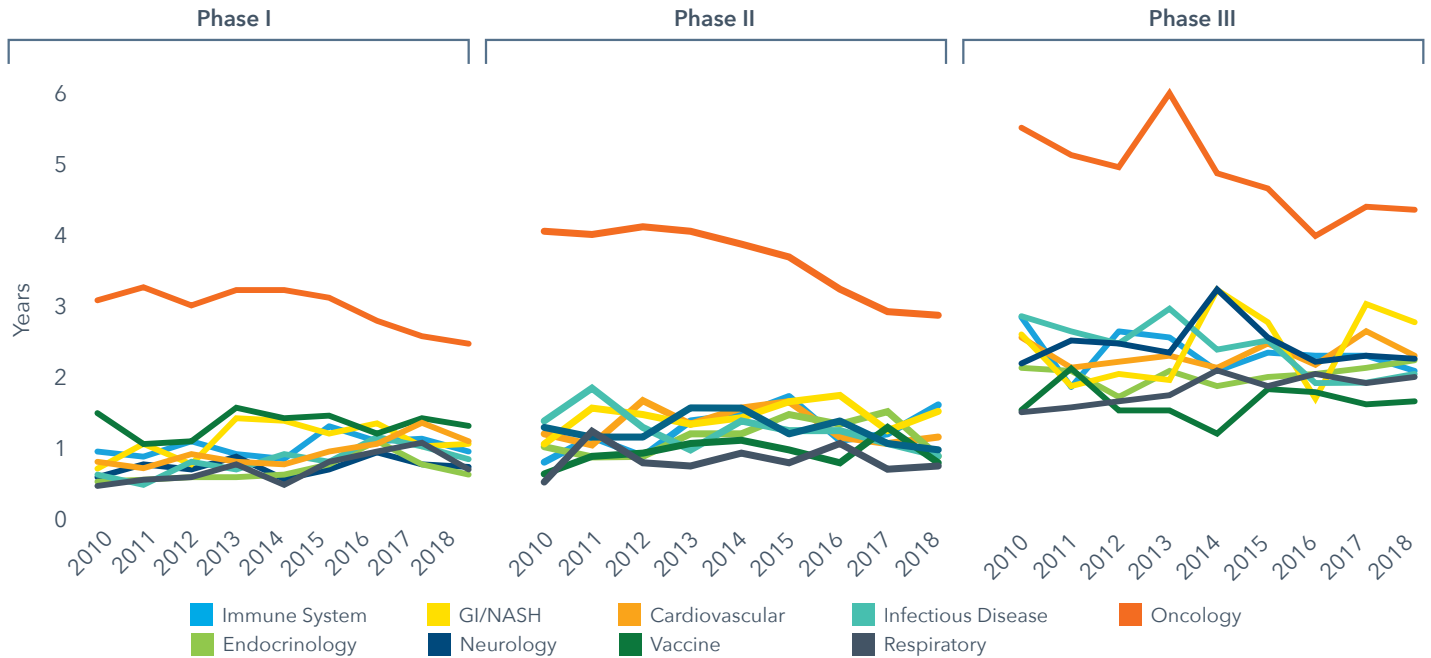
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Trial attributes that can be considered measures of clinical development complexity include five key areas: number of eligibility criteria, endpoints, trial sites, countries and patients participating in the trial.
- These attributes were measured and indexed across therapy areas to create an overall complexity metric to allow comparison across therapy areas and years.
- In 2018, the number of patients participating in clinical trials across nine selected therapy areas increased 10% compared to 2017; this growth is influenced by an increase of the number of patients in Phase III oncology and neurology trials, accounting for 20% of the sample.
- Clinical trial complexity has risen from 2010 to 2018, due to increases across all complexity attributes except the number of trial sites and countries, which did not increase.
- Phase I trial complexity has increased 6% since 2017 and 35% since 2013, while Phase II and Phase III trials have not changed.
- Phase I trials showed the greatest increase in complexity, with a 6% increase in 2018 and 35% increase since 2013, particularly in oncology and immune system diseases, but this growth is tempered by declines in other therapy areas, such as vaccine trials.
- Phase II trial complexity has been flat for the past several years for most therapy areas, although there has been a 23% growth in the complexity of oncology trials since 2010.
- Complexity for Phase III GI/NASH trials has tripled since 2010.
- Complexity in oncology is being driven by increases in endpoints and eligibility criteria, and offset by declines in the number of countries and number of sites.

Chart 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. Vaccine trials are infectious disease only. All others for Phase I = endocrinology, GI/NASH, infectious disease, neurology, respiratory; All others for Phase II = immune system, cardiovascular, endocrinology, GI/NASH, infectious disease, vaccine, neurology, respiratory; All others for Phase III = immune system, cardiovascular, endocrinology, infectious disease, vaccine, neurology, respiratory. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. All other is a weighted average.

Reported trial time in oncology has dropped an average of ten months from 2010 to 2018 across the three phases

Exhibit 21: Average Trial Duration by Phase and Therapy Area, 2010–2018



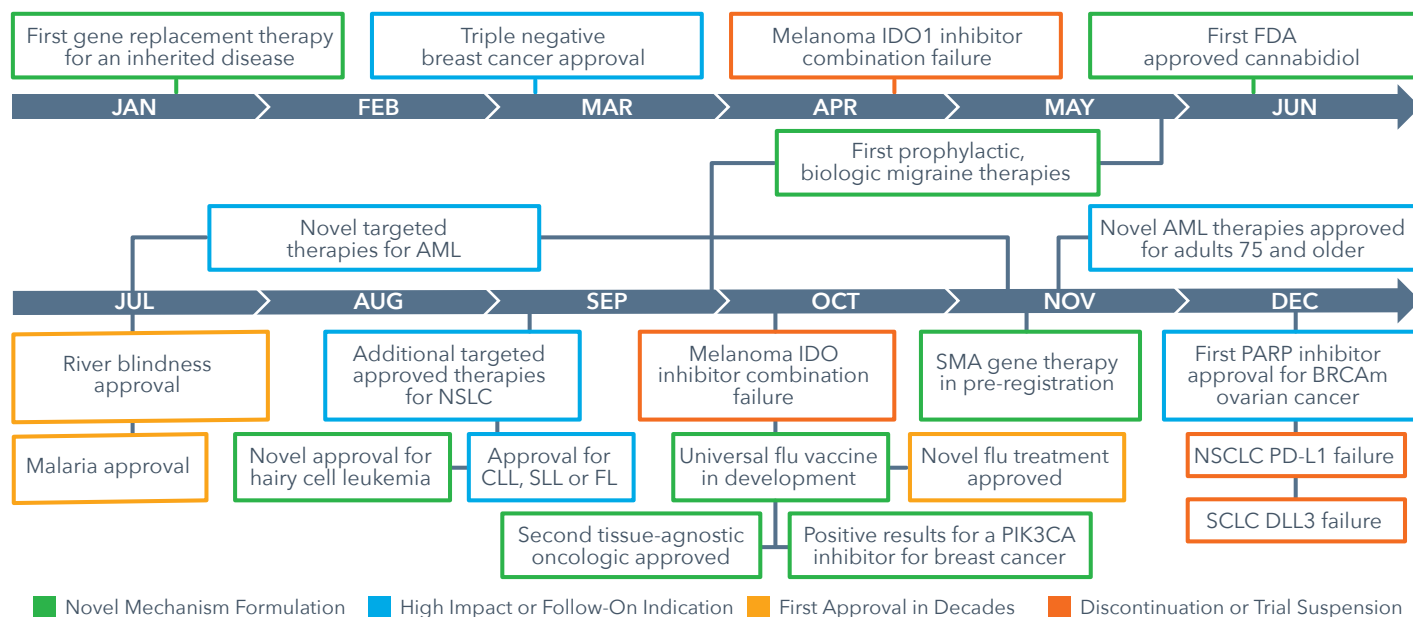
Source: Clarivate Analytics Cortellis, Mar 2019; IQVIA Institute, Mar 2019

- Within the past five years, the average trial duration, defined from the start of the trial to end of the trial, has varied across therapy areas.
- For Phase I trials, most therapy areas have shown an increase in the average trial duration, likely as more manufacturers are shifting trial design to look for signals of efficacy in earlier stages of development.
- Oncology shows a significant change in average trial duration since 2013, dropping seven months in Phase I, 11 months from Phase II and over a year and in Phase III studies.
- Other therapy areas, such as endocrinology, vaccines and respiratory show an increase in Phase III trial times, with respiratory trial duration for jumping 31% since 2010.

Chart 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.

Notable failures in cancer in 2018 were offset by large numbers of approvals and innovative breakthroughs across therapy areas

Exhibit 22: Select Positive and Negative Events at Registration and Clinical Levels, 2018



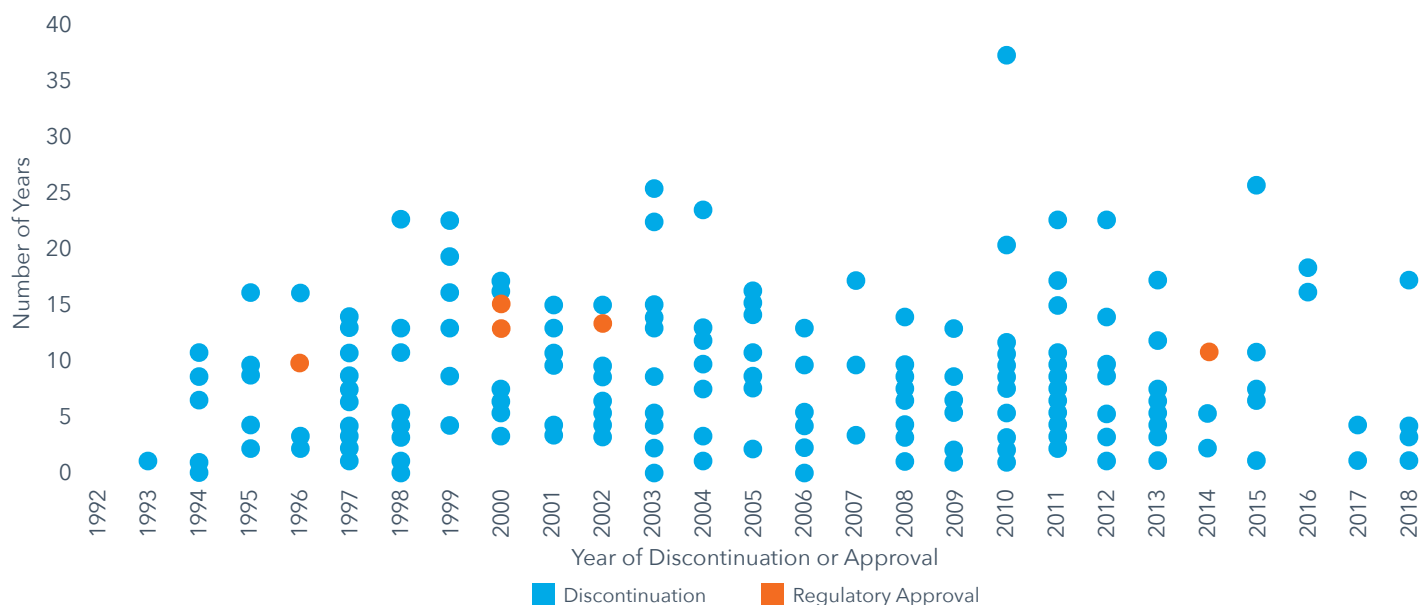
Source: Multiple public sources including 2018 FDA Drug Approvals, Nature Reviews Drug Discovery, Jan 2019; IQVIA Institute, Mar 2019.

- Oncology had a number of successes in 2018, particularly in AML, with the approval of three targeted therapies in an area with few approvals in recent years as well as approvals in patient subgroups for adults 75 and older.
- In breast and ovarian cancer, the PARP inhibitor olaparib became the first targeted therapy to receive approval for triple-negative breast cancer, a difficult to treat cancer with a poor prognosis, and olaparib became the first PARP inhibitor for ovarian cancer with a BRCA mutation. In addition, the Phase III therapy alpelisib demonstrated a near-doubling of progression-free survival in PIK3CA-mutant breast cancer.
- 2018 saw the approval of additional targeted treatments for EGFR-mutated NSCLC, ALK-positive NSCLC, and larotrectinib became the second product to receive a tissue agnostic indication.
- There were also setbacks in oncology in 2018, including a DLL3 targeted treatment failure in SCLC and the unexpected failure of the PD-L1 inhibitors in NSCLC. In melanoma, IDO inhibitor products performed poorly, both as monotherapy, and in combination therapies.
- In infectious disease, moxidectin was approved for river blindness, the first new treatment in over 20 years, and tafenoquine, a 40-year old drug, was approved in the United States for malaria. 2018 ushered in a novel flu antiviral, the first in over 30 years, and a universal flu vaccine entered Phase III.
- Three products with a new mechanism of action, calcitonin gene-related peptide (CGRP) antagonists, were approved to prevent both chronic and episodic migraines, the first advances in decades.
- In 2018, the first marijuana-derived pharmaceutical product, cannabidiol (Epidiolex), was been approved to treat Dravet syndrome, a rare form of epilepsy.
- For NGBs, the first gene replacement therapy for an inherited disease, voretigene neparvovec, launched, and the first gene therapy spinal muscular atrophy was filed.

Chart notes: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; SMA = spinal muscular atrophy; IDO = indoleamine 2,3-dioxygenase; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; FL = follicular lymphoma; PARP = poly ADP ribose polymerase; BRCAm = mutation in either BRCA1 or BRCA2; PD-L1 = Programmed death-ligand 1; DLL3 = delta-like protein 3; PIK3CA = alpha subunit of phosphatidylinositol 3-kinase; venetoclax received an additional approval in 2018, the drug was previously approved in 2016.

An additional four Alzheimer’s therapies were discontinued in 2018 bringing the total over the past ten years to over 85 failures

Exhibit 23: Number of Years Since Product’s First Patent Filing to Discontinuation or Regulatory Approval of Alzheimer’s Therapies



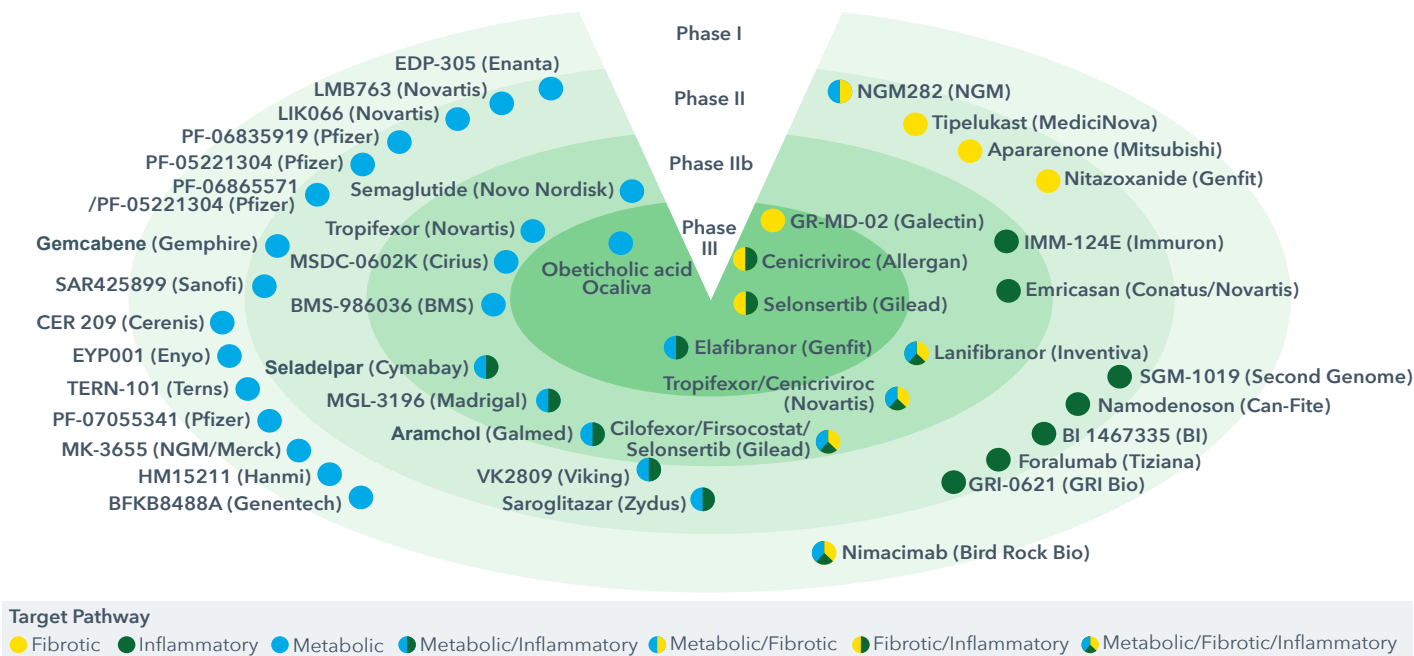
Source: IQVIA Pipeline Intelligence, Feb 2019; ARK Patent Intelligence, Feb 2019

- The global number of patients with dementia is projected to reach 82 million in 2030, and 60 to 80% of dementia patients may have Alzheimer’s disease.³
- Only five symptomatic therapies have received regulatory approval for the treatment of Alzheimer’s disease, and none treat the underlying disease.
- From 2008 to 2018, only one product received regulatory approval for Alzheimer’s, while 86 other development projects were discontinued. This product was notably also a combination of two previously approved medicines.
- The need for additional understanding of disease etiology, the need for better animal models, heterogenous patient populations, challenges with Alzheimer’s diagnosis, patient recruitment and endpoints all contribute to failures in the pipeline.
- For molecules under development for Alzheimer’s disease, the median time from patent filing to discontinuation of R&D program or approval was seven years from 1993–2018.
- From 1993–2013, the median time from patent filing to R&D discontinuation or approval was eight years, but from 2014–2018, the median time declined to 4.5 years, suggesting developers are increasingly discontinuing therapies before investing significant resources.
- In 2018, there were four discontinuations of early stage therapies due to Pfizer’s termination of its neuroscience program. 2017 saw similar company re-prioritizations, with Astellas and Eli Lilly discontinuing development of a Phase II and Phase I candidates, respectively.
- There were high profile clinical trial discontinuations in 2018 including, including pioglitazone, verubecestat and azeliragon.
- In March 2019, Biogen discontinued its late-stage therapy aducanumab, and in January 2019, Roche discontinued two Phase III trials for crenezumab. Both drugs targeted beta-amyloid and add to a growing body of evidence that this drug target may not prove to be efficacious.

Chart notes: The exhibit shows the time from patent filing to the end of clinical development, whether that was a discontinuation of the program or market approval; this does not show a discontinuation of a single clinical trial. Line extensions of marketed therapies are included with original global approval of the molecule.

Although currently there is no approved therapy for NASH, over 40 assets are in clinical development

Exhibit 24: Current NAFLD/NASH Pipeline with Targeted Pathways



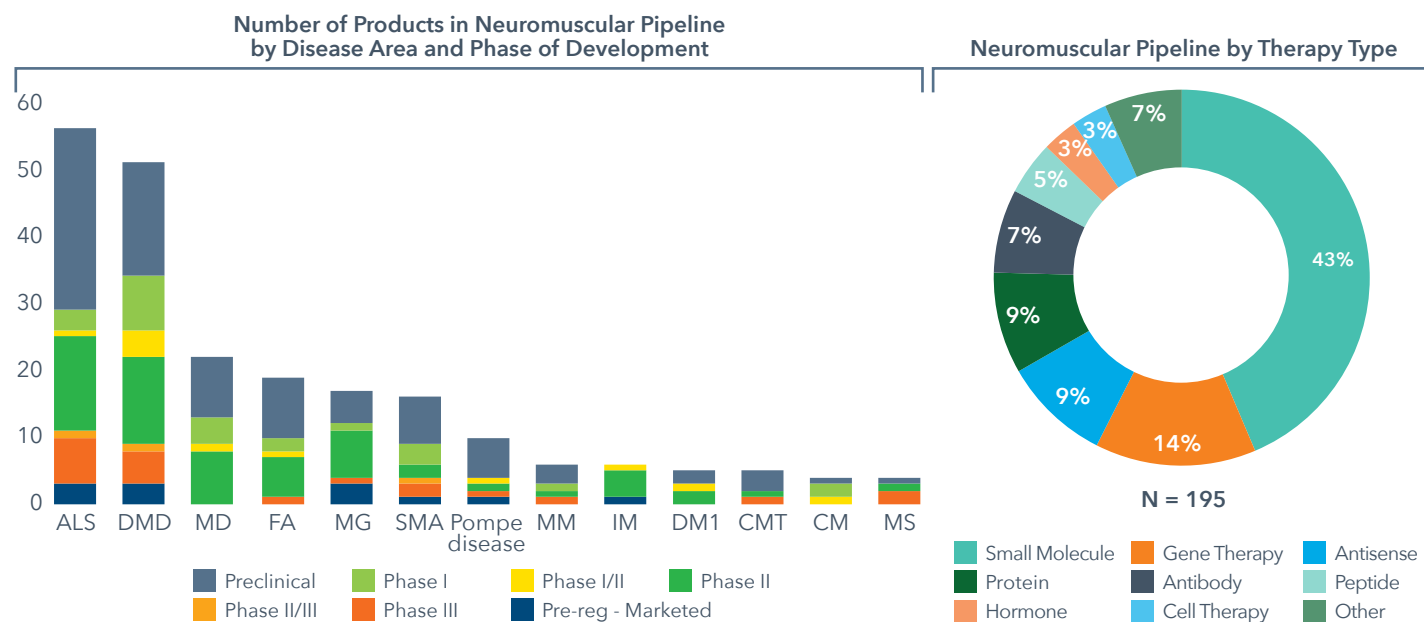
Source: Clinicaltrials.gov, Company websites, Jan 2011 IQVIA Consulting, Jan 2019

- Nonalcoholic fatty liver disease (NAFLD) and NASH are a complex disease continuum that is marked by hepatic fat accumulation, fibrosis and potential to progress to liver failure or cancer, if left untreated. Current epidemiological studies suggest approximately 42 million people in the United States have NAFLD, and approximately 20% of those have NASH.
- Disease manifestations begin as NAFLD, wherein hepatic steatosis is present and without evidence of hepatocellular injury. As the disease progresses, a diagnosis of NASH is conferred.
- Diagnosis of NAFLD/NASH still relies on expensive testing, such as imaging or liver biopsy, which introduce interpretation bias, making NAFLD/NASH difficult to diagnose.
- The development and progression of the disease is more common in patients with obesity or Type-2 diabetes, worldwide epidemics that are currently on the rise. As a result, there is a growing unmet need for NAFLD/NASH treatments.
- There is yet to be any standardization across trial primary endpoints, and no standard of care currently exists. Physicians currently rely on off-label treatment with generic products, such as pioglitazone, to address patient needs.
- In NASH, nine new drugs were added to the late-stage pipeline as drugs with several mechanisms of action continue to show promise in research. Current clinical efforts to address the unmet need of NAFLD/NASH include targeting three different pathways: metabolic, fibrotic and inflammatory.
- The early stage pipeline is largely focused on metabolic products, while those in late-stage development are largely combinations of fibrotic and inflammatory interventions. A majority of the late-stage pipeline includes products incorporating all three efforts, in an attempt to address all facets of this complex disease. The outcome of these studies will determine the overall value of single-mechanism products in development.

Chart notes: NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

A broad pipeline is emerging across neuromuscular diseases across all phases with a concentration in ALS and DMD

Exhibit 25: Neuromuscular Disease Pipeline by Phase and Type of Therapy



Source: Understanding Neuromuscular Disease Care: Current State and Future Prospects, IQVIA Institute for Human Data Science, Oct 2018

- The growing understanding of the underlying genetic components and molecular pathways of many neuromuscular disorders have helped to identify promising drug targets, and R&D activity in this space has grown rapidly in the past five years.
- The number of molecules in clinical development for neuromuscular diseases increased five-fold from approximately 20 in 2013⁴ to just under 200 preclinical through Phase III candidates as of April 2018, with R&D activity heavily concentrated in ALS and DMD.
- As of April 2018, 43% of the neuromuscular disease pipeline were small molecule therapies, although combined, gene and antisense oligonucleotide therapies made up almost a quarter of the pipeline at 23%.
- Antisense oligonucleotides are synthesized, single-stranded oligonucleotides that can modify RNA with the effect to either reduce, restore, or modify protein expression.⁵ In 2016, eteplirsen (Exondys 51) was the first antisense product to receive approval from the FDA for DMD. Nusinersen (Spinraza) is another antisense product approved by the FDA in 2016 for the treatment of SMA.
- Current pipeline strategies for ALS focus on the targeting of subtypes of ALS with gene therapies, neuroprotection and modulation of neuroinflammation and oxidative stress pathways being the most prominent.
- The most recently approved ALS medication was edaravone (Radicava) in 2017; 22 years after the last ALS drug was approved. Edaravone is a small molecule therapy thought to have anti-oxidant activity in ALS and has been shown to modestly slow disease progression.

Chart notes: Products indicated for >1 disease area are represented multiple times. ALS = amyotrophic lateral sclerosis; DMD = Duchenne muscular dystrophy; SMA = spinal muscular atrophy; FA = Friedreich’s ataxia; MD = Other muscular dystrophies (Becker muscular dystrophy, congenital muscular dystrophy, facioscapulohumeral muscular dystrophy, limb girdle muscular dystrophy, oculopharyngeal muscular dystrophy); MG = myasthenia gravis; IM = inflammatory myopathies (dermatomyositis, polymyositis, inclusion-body myositis); CMT = Charcot-Marie-Tooth disease; CM = congenital myopathies; MM = mitochondrial myopathy; DM1 = myotonic dystrophy type 1, CM = congenital myopathies, MS = other myasthenic syndromes (LEMS, congenital myasthenic syndrome).

Drivers of change in clinical development

- Eight key trends are influencing aspects of trial design, duration and success, including digital health and mobile technologies, curated real-world data sources, predictive analytics and AI, shifts in types of drugs being tested, biomarker test availability, shifts in the regulatory landscape, increased focus on patient-reported outcomes and pools of pre-screened patients/direct-to-patient recruitment.



By enabling the capture of drug efficacy and safety data remotely, digital health technologies are expected to improve patient safety, enable virtual trial formats and ease site work burden.



An increased focus on patient-reported outcomes will shed new light on patient experience and drug efficacy and safety outside the clinical setting, and lead to accelerated trial times as endpoints shift.



Real-world data (RWD) will be used to optimize trial design, speed trials by aiding in investigator and site selection, and will enable new trial designs by acting as virtual control arms and supporting pragmatic, adaptive and RWE registry trial designs.



Predictive analytics and artificial intelligence (AI) will mine data to identify new clinical hypotheses to test, reduce trial design risks and speed enrollment by identifying protocol-ready patients or predicting which patients have disease and may be eligible.



Shifts in drugs to targeted therapies and Next-Generation Biotherapeutics will improve efficacy and success rates and have accelerated development timelines, but will require longer-term patient follow up.



The increased availability and ease of biomarker testing will help narrow patient populations to those more likely to see effect, resulting in improvements in efficacy, safety and success.



Changes in the regulatory landscape will further the adoption of precision medicine approaches, novel trial designs and endpoints and provide means for accelerated drug approvals and regulatory success.



Availability of pools of pre-screened patients and direct-to-patient recruitment will facilitate trial recruitment and hitting of accrual targets, decrease trial duration and lead to accelerated market availability.

- The timing of trends is similar with all trends reaching their peak impact within 2.5-4.0 years.
- All trends were considered to have a high likelihood with the probability of impact ranging between a 74-85%.
- While regulatory shifts are the most likely to have an effect on clinical development, with an 85% likelihood of impact across therapy areas, changes are also expected to impact more slowly than other trends.
- Changes in scientific advances - shifts in drug types being tested and biomarker use - are next most likely to impact clinical development and will affect most therapy areas in the near term.
- Many of the therapy areas with the most complex trials will see impacts of these trends within three years.

Assessing the Impact of Clinical Development Trends

The IQVIA Clinical Development Trends Impact Assessment was conducted from June–July 2018 in the form of a questionnaire completed by 24 internal IQVIA therapy area experts. Between one and three responses were received per therapy area and at least two for large therapy areas excepting respiratory, where only one response was received. The assessment questionnaire asked respondents to assess how eight drivers of change, shown below, would impact the clinical trials conducted in their specific therapy area.

-  **1. Application of Digital Health / Mobile Technologies**
-  **2. Increased Focus on Patient-Reported Outcomes**
-  **3. Emergence of Curated Real-World Data Sources**
-  **4. Use of Predictive Analytics and Artificial Intelligence**
-  **5. Shifts in Types of Drugs Being Tested**
-  **6. Availability of Biomarker Tests**
-  **7. Changes in the Regulatory Landscape**
-  **8. Availability of Pools of Pre-Screened Patients / Direct-to-Patient Recruitment**

The Clinical Development Trends Impact Assessment asked for the respondents' perspectives on the impact, in the short, medium and long term of these key trends along with a quantitative assessment for their therapy area of:

1. The likelihood the trend would change clinical development
2. The timing of that change
3. The phase of trials it would impact
4. The extent to which these trends would change clinical development via assessment of impact on the various elements of effort, success and productivity included in our study, namely:
 - a. Trial scope/size (i.e., number of patients, sites, countries)
 - b. Design elements (i.e., numbers of eligibility criteria and study endpoints)
 - c. Trial duration
 - d. Likelihood of trial success (number of trials with positive results)

This data was then used to model future impacts on effort, success and productivity for each therapy area. Respondents were additionally asked to provide color commentary on how trends would impact their therapy area. That narrative has been incorporated into this section of the report.

DRIVERS OF CHANGE IN CLINICAL DEVELOPMENT

Application of Digital Health / Mobile Technologies

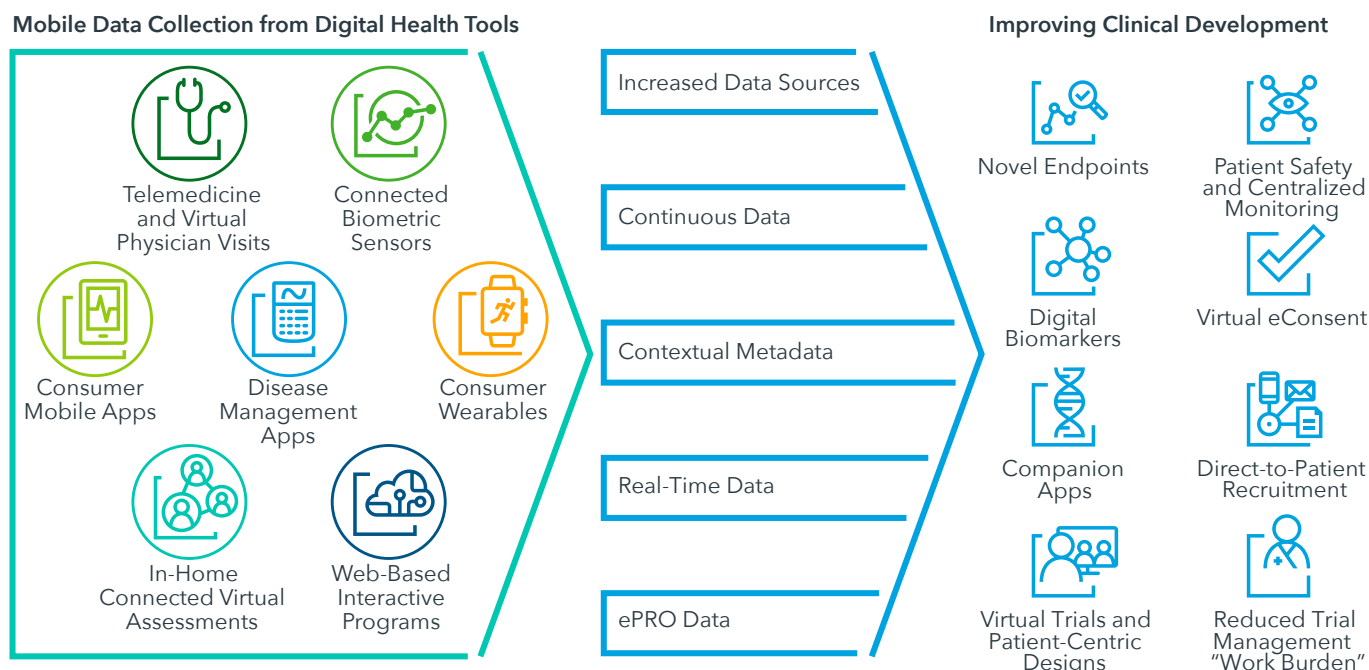
Digital health technologies, including mobile health (mHealth) apps, wearable sensors, telemedicine and other software tools, are finding novel uses in clinical development. Sensors can be used to directly record biometric health measurements in a real-world setting in real-time, while apps and other devices can track patient-reported outcomes (PROs) or experience measures (PREMS), which can be shared with clinicians. Novel “digital biomarkers” of health that correlate to disease severity and outcomes are being built on top of wearable activity monitors (e.g., Fitbit) and other biosensors using algorithms, and offer possibilities for disease monitoring.⁶ Telemedicine, using phone and video capabilities, allows clinical assessments to be conducted remotely as virtual patient visits and visually confirms patient status. Finally, in its most basic form, using digital tools to send reminder messages to patients can maintain patient engagement and encourage specific behaviors, such as drug adherence.

As these digital health technologies find novel uses in clinical development, they are specifically expected to:

IMPROVE THE CAPTURE OF DRUG EFFICACY AND SAFETY DATA

Experts see centralized patient monitoring growing across most therapy areas in the coming years. In movement disorders, such as Parkinson’s disease, and in psychiatry, cardiology and rare diseases, digital biomarkers of health (tracking of movement, handwriting, voice patterns, touchscreen use-patterns, etc.) offer novel “functional” endpoints tied to meaningful real-world clinical benefit. These may also replace some traditional clinical endpoints or PROs. For instance, in allergy trials, the use of wearable actigraphy for sleep quality is easier to collect and will offer higher-quality data than sleep questionnaires.

Exhibit 26: Digital Health Applications Transforming Clinical Development



Source: IQVIA, Mar 2019; IQVIA Institute, Jun 2019

DRIVERS OF CHANGE IN CLINICAL DEVELOPMENT

FACILITATE THE COLLECTION OF PROs

Digital tools will better assess patient experience and quality of life and help build patient perspective into clinical trials. Electronic PROs (ePRO) – typically digital questionnaires – will be widely used across therapy areas tracking pain, urinary and vasomotor symptoms in urology and reproductive health, vomiting in infectious disease trials, and pain, nausea and tiredness in cancer patients. By making it easier for patients to complete than traditional questionnaires, and enabling reminders, digital tools will likely make data reported by subjects more accurate, improve data quality, and increase patient engagement to increase timeliness of data reporting and reduce missing data points.

IMPROVE PATIENT SAFETY WITHIN A TRIAL SETTING

Patient experience data that is tracked in eDiaries or by wearables can then be conveyed as data in real-time to trial staff to trigger appropriate physician contact or activate electronic instructions (e.g., collect a respiratory swab). This feedback loop could enable trial participants to receive rapid physician support in the event of adverse events, thereby improving trial safety – particularly in oncology and neurology – and decreasing the likelihood of patient attrition. Overall, this type of rapid adverse event alert system is expected to improve trial success. This real-time safety data will also facilitate trials in high-risk (e.g., HIV positive) and vulnerable (e.g., neonatal) populations within infectious disease, enable drug developers to stop trials with negative signals much faster, and generally allow for more complex trial designs, such as adaptive trials where experimental treatments are personalized to patients' tolerances.

ENABLE VIRTUAL PATIENT VISITS AND SITE-LESS TRIAL FORMATS, IMPROVING PATIENT EXPERIENCE

Digital tools offer to improve patient experience and make patient participation more convenient through virtual assessments, reducing the number of site visits required for participation, and associated trial dropout

rates. These formats are also likely to be used for contagious diseases trials where patients are generally advised not to visit the clinic, and vaccine and allergy trials, where multi-year follow-up of symptoms may be among the endpoints. Relieving the burden patients face to access trial sites will be significant for neurology trials, as patients with mobility-limiting conditions, such as Alzheimer's disease, Parkinson's disease or multiple sclerosis, may not be able to easily access a trial site. Similarly, it will facilitate the conduct of trials in developing countries or remote sites, particularly in vaccines and infectious disease, where internet is available but travel to sites may be challenging.

REDUCE TRIAL MANAGEMENT "WORK BURDEN" AT CLINICAL SITES AND SPEED RECRUITMENT

Through the adoption of digital tools for trial management, and eConsent enrollment platforms, work burden and recruitment rates are expected to improve in GI/NASH, oncology and cardiology, among other areas. Digital health apps are expected to enable larger patient numbers to be recruited in a shorter time-period. Further, as digital technologies allow for data to flow passively from multiple sources and be pooled in a central data hub for analysis, sites will cease to be the primary source for all data collection and data entry, thus reducing staff and site burden. Overall, this is expected to reduce trial execution costs in some areas including neurology.

CHALLENGES

Although the ability of digital health tools to offer real-time continuous patient monitoring comes with unique data collection challenges, at times generating large amounts of data that can increase data processing costs and analysis time.

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Increased Focus on Patient-Reported Outcomes

As patient voices are more loudly heard through advocacy groups, social media and blogs, efforts are growing to include patients in the process of designing clinical trials (e.g., Patient-Centered Outcomes Research Institute)⁷ to ensure patient outcomes and experience measures are included as endpoints in trials. The intent of incorporating these in trials is generally to include information about these outcomes measures on drug labels, and to provide a more holistic view of drug benefit, including impact on patient quality of life and function. Overall, this trend reflects a shift in the way the medical community values information reported directly by patients. As collection of PRO measurements increase, they will also be increasingly collected electronically using mobile ePROs or wearables.

In clinical trials, PROs are specifically expected to:

PROVIDE ADDITIONAL VIEWS OF DRUG EFFICACY AND SAFETY OUTSIDE CLINICAL SETTINGS

PROs are a growing component of clinical trials across therapy areas, including autoimmune and GI trials, and are already a strong component of allergy, oncology and rare disease trials. Between 2012 and 2016, approximately 22% of orphan drugs approved by the EMA incorporated PROs,⁸ and in oncology, 70% of indications for 49 EMA and FDA approved drugs included PRO data in their regulatory submissions.⁹ PROs are currently used in Phase II and III studies in oncology, and are valuable to describe patient symptoms and function, such as to better demonstrate the tolerability of an anticancer agent. In rare disease trials, PROs are expected to provide a more complete view of the effects of a drug. For example, PROs have changed the landscape in sickle cell anemia trials, where focus has shifted to pain reported by patients at home rather than in the hospital, better elucidating “real-world” experience.

BECOME MORE ACCEPTED BY REGULATORY BODIES AND INFLUENCE DRUG LABELING

Although PRO endpoints are already incorporated into clinical trials, regulatory bodies are increasingly open to accepting novel PRO endpoints and including them in product labels.¹⁰ Experts in NASH even suggest clinical trials will begin to use PROs as the primary outcome. For oncology, quality of life assessments and new endpoints that measure novel aspects of clinical benefit are expected to become the basis for some new approvals.

ACCELERATE TRIAL TIMELINES

The use of some patient-centered endpoints will enable shorter trial durations across Phase II and Phase III cardiovascular and reproductive health trials. In cardiovascular trials, for example, where the goals of cardiovascular and heart failure care are more patient-centered (e.g., exercise and quality of life) rather than achieving longer survival, if PRO endpoints are accepted as primary outcomes measures, trial duration may shorten. This is because these types of endpoints do not require the lengthy study durations of standard cardiovascular outcome trials (CVOT). Although PROs may improve the likelihood of showing positive results in cardiovascular and endocrinology trials it may also increase the number of eligibility criteria; in this specific case, patients will need to be literate to respond to questionnaires and be able to exercise.

INCREASE PATIENT ENGAGEMENT BOTH DURING AND POST-TRIALS, WITH BENEFITS TO STUDY SUCCESS AND REIMBURSEMENT

In general, inclusion of PROs tends to more meaningfully illuminate the impact of a drug on patients' lives, thereby increasing the value of clinical trials to patients. Cardiovascular, neurology, endocrinology and respiratory experts note for trials with PROs, patients develop a greater interest in and better understanding

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of the personal benefits of a novel treatment. They, therefore, tend to be more involved post-approval in health technology assessment (HTA) submissions. Further, the inclusion of PROs in studies also tends to lead to inclusion of more patients in advisory boards and patient advocacy groups, which then become key players in promoting the study's success.

TRACK ADVERSE EVENTS AND PATIENT PERCEPTION OF DRUGS AFTER APPROVAL TO GUIDE PUBLIC HEALTH INITIATIVES

Once a drug reaches the market, PROs can help track safety and adverse events in larger, real-world post-approval studies,¹¹ such as increased safety monitoring after vaccinations. These data are more likely to capture true effects of a novel drug, including adverse events that may impact a subject's daily life. They can also gather patients' thoughts on which vaccines are perceived as more or less desirable, and use this information to guide public health messaging and campaigns. For example, the acceptability of maternal immunization against flu is often cited as a barrier among stakeholders,¹² and assurances of safety can help to support a patient's decision to receive a vaccination.

CHALLENGES

While patients may be happy to share their experiences through PRO assessments, only through improved collection methods, such as electronic collection, will the burden of PROs on patients be reduced and response rates improved. Patient adherence to traditional assessments tends to be poor and thus finding easier ways of collecting data - for instance, through digital health tools rather than traditional questionnaires - will be critical to improve data quality, reliability and reduce missed data points.

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Emergence of Curated Real-World Data Sources

Over the past five years, as big data gathered in real-world healthcare settings has become more prevalent, robust and more skillfully curated, it has seen increased use across the healthcare industry as real-world evidence (RWE). Various data sources including electronic health records (EHRs; collected by care providers and medical centers), medical claims data, and disease registries can be used to support population-based research to better understand how cohorts of patients respond to medicines outside controlled clinical trial settings, how drug outcomes vary across diverse populations, or understand more about the natural course¹³ or heterogeneity of disease. Claims data or clinical trial databases can further be leveraged to understand details about the care provided at clinical sites, and physicians and their treated populations to determine their value to initiatives, including clinical trials.

Real-world data (RWD) is expected to have an impact on many aspects of clinical development programs, particularly around patient selection and trial design. It is specifically expected to:

HELP MANUFACTURERS DESIGN TRIALS WITH OPTIMAL PROTOCOL SPECIFICATIONS

RWD is invaluable for demonstrating the effect of an investigational product in a real-world setting that may differ from results found in a clinical trial, and this type of data can drive protocol design and especially affect Phase III pivotal trials across therapy areas. In new disease segments or rare diseases, it can help to create right-size trials to detect a “treatment effect” by clarifying the baseline disease progression or symptoms for untreated patients. For instance, the analysis of RWE may suggest the need to increase or decrease patient numbers, adjust inclusion/exclusion criteria to select for the right population, or identify endpoints for rare diseases. RWD can also be used to remove selection

bias from clinical studies and more accurately represent the heterogeneity of disease population (e.g., in reproductive health trials).

ACCELERATE TRIALS BY AIDING IN INVESTIGATOR AND SITE SELECTION AND RECRUITMENT

By identifying where eligible patients are located or care facilities (e.g., patients with high risk of surgical site infection for infectious disease trials or sites with large volumes of such surgeries), RWD will improve selection of high-quality sites and investigators with larger pools of patients, and may expand the number of referring physicians. This gain in recruitment efficiency is critical to therapy areas recruiting large numbers of patients like oncology and neurology.

PROVIDE FEASIBILITY FOR NEW TRIAL DESIGNS

RWE will enable pragmatic and adaptive trial designs, as well as RWE registries, that will affect oncology and GI and many other therapy areas. For instance, in the infectious disease space, pragmatic trials, which test medicines in routine clinical practice settings, may show investigational product efficacy and safety in a real-world setting not otherwise detected in standard clinical trials, thereby driving trial success and speeding approvals.

SERVE AS COMPARATORS AND VIRTUAL CONTROL ARMS IN CLINICAL TRIALS

Rather than running a traditional placebo-control trial, patients on a therapy are matched to historical controls or prospectively matched to patients represented in RWD sources (e.g., randomized registry trials in the cardiovascular device space). This can be valuable in rare and underserved diseases and oncology trials, where randomization to a control arm might deny access to new treatments and spur ethical issues, and across Phase III trials in neurology, oncology, allergy,

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infectious disease and cardiology device trials, where recruitment can be an issue.¹⁴ The opportunity to leverage such hybrid RWD/RCT studies is viewed positively across therapy areas, and the FDA has also signaled it will additionally accept the use of RWD for initial approvals of new drugs addressing high unmet need.¹⁵

TO TRACK LONG-TERM PATIENT OUTCOMES

RWD can be used as an alternate source of drug efficacy and safety data to RCTs. In vaccines, where some diseases may require only one trial for approval, RWD may be used to support or validate the endpoints/outcomes seen in the traditional clinical trial by monitoring long-term safety data after introduction of a vaccine (e.g., infant vaccines).

PROVIDE ADDITIONAL EVIDENCE FOR POST-APPROVAL LABEL EXPANSIONS, LONG-TERM EFFICACY, OR OTHER IMPORTANT CLINICAL QUESTIONS

Examining off-label drug use in RWD, or identifying the heterogeneity among the population using them, can help guide hypotheses about further areas where a current drug or new formulations might be efficacious or safe. It can be especially helpful to answer such important clinical questions and to confirm a hypothesis especially in instances where running a standard, randomized trial is not possible due to prohibitive timelines or other factors.

CHALLENGES

There are data challenges associated with the incorporation of RWD into clinical development programs that will need to be overcome. For example, RWD in oncology lacks many of the datapoints often used in controlled clinical trials, such as biomarker data and consistent disease assessment data (e.g., RECIST¹⁶). In allergy trials, there are similar issues around consistent capture of currently-used outcomes data, which are not currently coded into big data sets, and fears that this may lead to a decrease in study outcomes or difficulties defining a comparable population.

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Use of Predictive Analytics and Artificial Intelligence

Artificial intelligence (AI), machine learning and other predictive technologies can be used to obtain value from big data in healthcare and derive evidence-based insights to help guide decisions. By leveraging a variety of healthcare data sources on drug candidates, disease populations, clinical sites, or groups of patients or physicians, AI can help build models to identify desirable characteristics among a set, identify changes that can be made to optimize actions or efficiency, generate new hypotheses, predict future outcomes and inform best decisions.

Combined with RWD, the insights from predictive analytics and AI will help shape the design specifications of clinical trial protocols and increase the quality and efficiency of studies. Predictive analytics and AI are likely to prove most valuable in Phase II and III trials, and in highly competitive areas of the market, such as rheumatoid arthritis and spondyloarthritis drugs in the autoimmune space.

Specifically, it will:

GENERATE NEW HYPOTHESES TO TEST CLINICALLY

One of the key applications of predictive analytics and AI will be to generate new clinical hypotheses from RWD databases (e.g., EHRs) and to later verify these through prospective clinical trials. This is likely to shift the focus of trials and these new studies may see higher rates of success, already being supported by more evidence than typical, early trials. Similarly, when applied in the discovery phase, AI may strengthen computational models that predict links between drug structure and activity/efficacy/safety (i.e., SAR) to improve success rates.

REDUCE RISK TO TRIALS BY IMPROVING STUDY PLANNING

Whether by predicting enrollment trajectory, determining peak trial screening rates, or identifying other limitations or specifications that need to be considered to optimize clinical trials, predictive analytics can make trials more efficient and improve success rates. For example, enrollment is a key area where AI will be used to predict success. Overall, when AI predicts trial success across all phases, it will increase the confidence of success for outcomes and later approval.

SPEEDING ENROLLMENT BY GUIDING PATIENT IDENTIFICATION

Predictive analytics can support trial recruitment by better identifying protocol-ready patients within RWD or registry data designated for that purpose, such as identifying patients considering clinical trial enrollment and voluntarily enrolling. For instance, machine learning algorithms can create optimized matches of individual clinical data (including biomarkers and barriers to enrollment) from EHR platforms to existing institutional and non-institutional clinical trials (CT). In NASH, neurology and oncology studies this trend is expected to reduce enrollment time and screen-failure rates. Additionally, at the stage of diagnosis, AI will be paired with genomics to allow for early diagnosis of patients with rare disorders who might otherwise not be identified. This may have a particularly large impact in recruitment for rare pediatric illnesses. Other algorithms will allow for better access to patients earlier in the course of disease that is likely to impact prevention trials for progressive diseases, including those in the neurology space, such as Alzheimer's disease or mild cognitive impairment (MCI). Use for trial recruitment in some therapy areas will be limited by the amount of in-person clinical assessment needed of disease status (e.g., allergic diseases) and response to treatment.

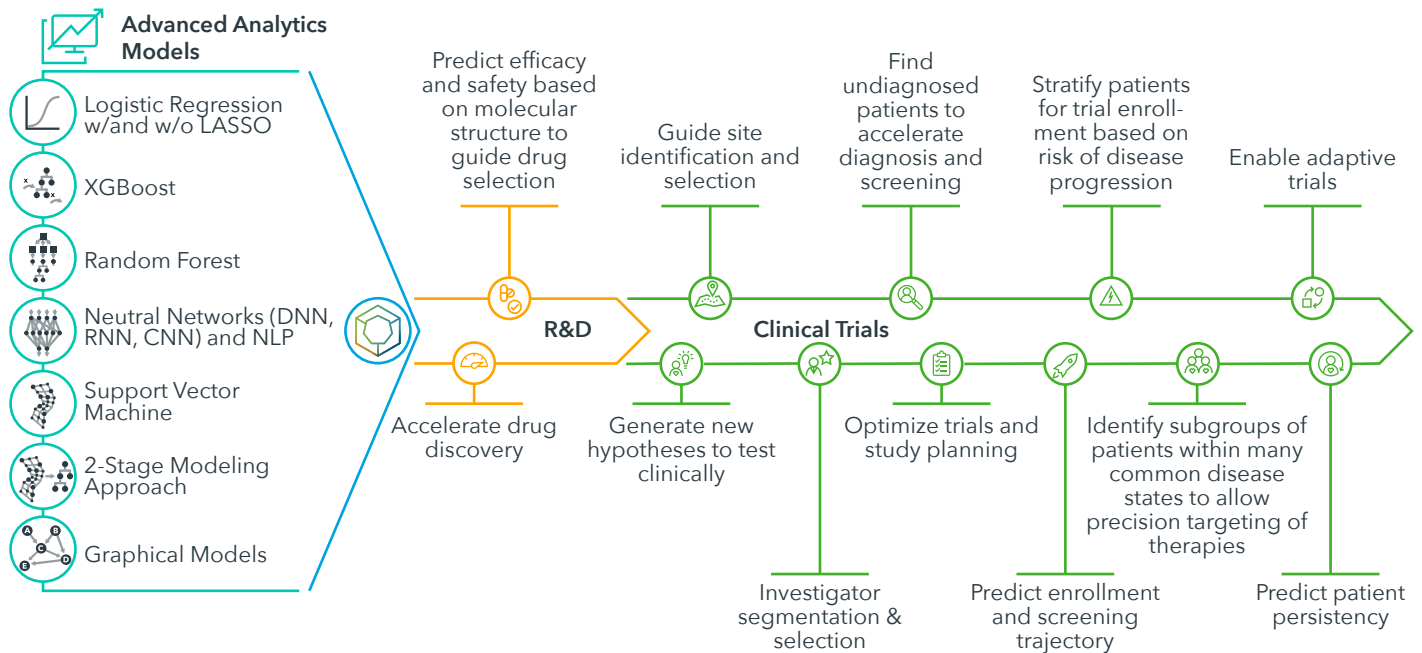
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ENABLE PRECISION TARGETING TO BETTER DETECT A TREATMENT EFFECT

Because most diseases have some degree of heterogeneity, predictive analytics and AI will identify subgroups within many common disease states to allow for precision targeting therapies (i.e., precision medicine) and increase success rates. This will enable studies to be performed on or include, pre-defined patient subgroups, such as patients with genetic markers shown to increase the risk of tumor development, and is likely to create or identify more rare disorders. This trend is likely to impact all phases, with even early Phase I trials seeing dosing tailored more effectively to subpopulations of patients and later phases seeing the recruitment of targeted subjects more likely to see an effect. This could increase the

efficacy signal and allow for decreased sample sizes – something that will have an impact on GI and infectious disease trials. The trend is already being assessed in the neurology space, such as in acute stroke, where AI can assess disease severity based on imaging and may help determine which intervention will be best for a specific patient’s treatment (similar to how it has already been used in trials determine proper care in acute stroke trials in neurology). In oncology, AI and machine learning will eventually link patients with a targeted therapy based on a specific genomic mutation, alteration or gene translocation. Limitations exist in other therapy areas, such as in the allergy space, where food allergy symptoms are not well predicted by standard test results, and needed data relating to environmental allergen exposure can be absent from data sets.

Exhibit 27: Predictive Analytics and AI Driving Value for Clinical Development



Source: IQVIA Advanced Analytics, Feb 2019; IQVIA Institute, Mar 2019

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PREDICT WHICH CLINICAL SITES ARE MOST LIKELY TO RECRUIT AND PERFORM WELL

By predicting rates of disease in a local population over time, predictive analytics can help guide site selection to those sites likely to recruit rapidly, shortening timelines. This can be especially critical in therapy areas where large numbers of patients are required, such as cardiovascular trials, as well as endocrinology. Predictive analytics can also reduce trial size by selecting sites where it is easier to detect endpoints. For example, clinicians say AI and predictive analytics can locate hotspots for infections so vaccine trials that track infection rates (e.g., Ebola), can select sites in those locations and run smaller trials with fewer subjects.

ENABLE NOVEL TRIAL DESIGNS INCLUDING ADAPTIVE TRIALS

Better insight and better predictions through AI will optimize trial design and scope to allow greater diversity in study designs. This may allow some trials to be more modest and others more expansive, especially in women's reproductive health. Adaptive trials in particular will improve efficiency and lead to early approval with smaller patient samples.

CHALLENGES

AI outputs will only be as good as the accuracy and robustness of the information feeding these predictive models. The long-standing promise of AI improving clinical trial development has not been borne out to date, and IQVIA experts offered mixed assessments on the likelihood of AI impacting their respective therapy areas, including allergy. This is in part attributed to issues obtaining adequate and consistently-coded data sources for modeling, which is expected to limit overall impact.



Shifts in Types of Drugs Being Tested

Continued advances in basic science and a growing understanding of disease bio-processes are enabling the development of drugs targeting new disease pathways and molecular targets. The types and mechanisms of drugs under development are therefore changing, as well as the strategies they take to treat disease. These include shifts from symptomatic therapies, which minimize disease symptoms, to disease-modifying therapies that slow or halt disease progression, and are better enabled by earlier identification of disease, as well as the emergence of Next-Generation Biotherapeutics, which include cell-based therapies, gene therapies and regenerative medicines (notably induced pluripotent stem cells (iPSC) and CRISPR/Cas). Additional technical advancements have also made biologics increasingly easy to develop and manufacture, resulting in a growing percentage of the drug pipeline being created using recombinant DNA technology and accounting for almost a third of new drug approvals.^{17,18}

Shifting drug types are expected to lead to improvements in patient survival time and overall patient quality of life, as well as revolutionize the standard of care in oncology for most tumor types. For example, genomics is becoming a starting point in drug development, including the screening of cancer genome databases and protein structure databases, which aids in matching novel drug targets to specific cancers.^{19,20} Specifically, in oncology, understanding the mechanisms of patient resistance to immunotherapy will help design strategies to prevent or treat resistant mechanisms.

Within clinical development, new drug targets are likely to:

HAVE GREATER EFFICACY AGAINST THE DRUGS' BIOLOGIC TARGETS LEADING TO IMPROVED SUCCESS RATES

Examples of shifts in types of targeted drugs being tested in oncology include: next-generation checkpoint inhibitors, cancer vaccines, immunomodulators, oncolytic viruses, bispecific monoclonal antibodies, new small molecules and identification of T-cell targeted immunomodulators, which include chimeric antigen receptor drugs developed for solid tumors rather than blood cancers. Where new actionable targets are identified, the earlier phases of oncology clinical development programs will be the most impacted. In immuno-oncology, they will see the dose escalation to toxicity (a linear dose response curve) often no longer holds.

USE NON-TRADITIONAL DEVELOPMENT PATHWAYS WITH INCREASED TRIAL COMPLEXITY BUT ACCELERATED TIMELINES

Although oncology experts explain that new types of drugs often can be tested using very similar trial designs, some new curative therapies may not flow through a traditional Phase I to Phase III approach, but will see increased use of novel trial designs, such as adaptive trials (e.g., in GI trials) that start as a single Phase I study that begins cautiously and expands to prove efficacy. For example, early stage immuno-oncology Phase I trials have begun to enroll over 1,000 patients with very long duration but yield data needed for registration. Curative therapies with high response rates may see approval with testing on only a few patients. In neurology, next-generation therapies will increasingly gain FDA regenerative medicine advanced

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therapy (RMAT) designation and see faster approvals with smaller sample sizes, but these benefits will be balanced by logistic challenges around trial execution.

INCLUDE NEXT-GENERATION BIOTHERAPEUTICS THAT MAY REQUIRE LONGER-TERM FOLLOW UP

In oncology, autoimmune, primary immune deficiency and infectious disease, genetically engineered cells, both autologous or allogeneic, are expected to play a significant role in the future. Stem cells will impact in cardiovascular disease and heart failure, where they will place a greater burden on enrollment. Perhaps the most significant impact across therapy areas will be in rare diseases – many of which are single gene disorders – where conditions that had no druggable targets are now being approached primarily with gene therapies and gene editing/correction. Overall, cell therapies and gene-therapies will likely require longer term follow-up on a large-scale basis.

INCLUDE MORE DISEASE-MODIFYING DRUGS THAT WILL LENGTHEN TRIAL DURATION AND ALTER ENDPOINTS

The testing of disease modifying drugs will shift study focus to earlier and preclinical stages of disease, particularly in neurology and reproductive health, as well as autoimmune therapies. For these drugs, the need to document a change over the course of disease is expected to require longer trials. Endpoints used in disease-modifying trials will alter to detect changes in disease severity over time, and may include increased biomarker measurement via lab testing and imaging. In neurology, where many conditions are challenging to treat at later stages and existing treatments address only patient symptoms, there is a strong shift towards disease-modification trials. However, this shift requires the successful identification and recruitment of early disease patient populations, which often still poses challenges. In neuropathic pain and in infectious diseases with long-term inflammatory symptoms, such

as in pneumonitis or systemic inflammatory response, disease-modifying therapies are also emerging and may help improve patient outcomes. In addition, preventative strategies may also affect types of study drugs: targeted cell entry receptor blockers to prevent infection, monoclonal antibodies to offer protection during high risk periods (e.g., seasonal infections or high-risk exposures) and biophages to address antimicrobial resistance.

SHIFT THE STUDY POPULATIONS ENROLLED ACROSS ALL PHASES OF DEVELOPMENT THROUGH TARGETED THERAPIES

In oncology, genomic profiling for specific genomic mutations, alterations or gene translocations, can help identify the optimal combinations of checkpoint inhibitors to use or the optimal scheduling of combinations, and help select patient populations most likely to respond. The immune system is a new area for targeted oncology products, with many novel and precise targets, as well as metabolic targets in tumor cells. Outside of oncology, NASH and autoimmune targeted therapies are expected to have increased effectiveness. In the cardiovascular space, precision medicine and more specific phenotyping of heart failure and other patients will lead to the inclusion of more specific study populations and improve results, especially in heart failure with a normal ejection fraction (HFpEF). However, the additional requirement of meeting genetic or biomarker entry criteria may decrease recruitment and lengthen study timelines.

AN INCREASE OF BIOMARKER-SPECIFIC THERAPIES

In oncology, biomarkers have enabled a shift to tissue-agnostic regulatory approvals through predictive biomarkers, as in the case of pembrolizumab and nivolumab in microsatellite instability high (MSI-H) tumors. The trend towards precision medicine therapies is expected to continue across numerous therapy areas including cardiovascular, immune system and NASH.

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SEVERAL THERAPY AREAS MAY SEE A SHIFT TO BIOLOGICS FROM SMALL MOLECULE THERAPIES FOR THE FIRST TIME

For some allergic diseases, biologics are becoming an option that will lead to greater treatment specificity and new disease targets, the first of which include immunotherapies for environmental and food allergies. Because biologic trials are more complex than those for traditional small molecules, there are challenges in conducting certain assessments and higher risks of adverse events from the investigational product. In infectious disease, the opposite is true, and lower risks are expected. For instance, the development of new drugs for antimicrobial resistance, such as bacteriophages, may lead to clinical trials with potentially fewer adverse events, as the use is more targeted. In infectious disease, this is being driven by the necessity to develop novel approaches to treat or prevent resistant bacterial and fungal infections, such as vaccines or monoclonal antibodies or antitoxins.

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Availability of Biomarker Tests

Along with a greater understanding of disease etiology and genetics has come a greater understanding of biomarkers linked to patient genetic or metabolic profiles, tumor genetics and disease pathology. Biomarkers can indicate the stage of disease, identify the subtype of disease, or reveal that a single disease could actually be considered several separate, less-common disorders. Predictive biomarkers can further stratify individuals by their susceptibility to a particular disease, determine whether their disease is expected to progress more slowly or rapidly, or predict whether they are more likely to respond to a specific treatment or have a specific side effect. A biomarker is considered “predictive” should the effect of treatment, side effects or dosing show a difference between those patients screened positive for a biomarker compared with those who show a negative screen. These predictive biomarkers therefore enable precision medicine approaches and generally allow diseases to be defined into more narrow subsets.

Within clinical development, greater uptake of biomarkers in clinical trials is likely to:

ALTER PATIENT ELIGIBILITY CRITERIA TO NARROWER POPULATIONS AND DECREASE SAMPLE SIZE

The use of genetic and other biomarkers to stratify individuals into subpopulations and recruit specific subsegments into trials is expected to increase. New drug trials are increasingly using precision medicine approaches and targeting narrower indications. While these more homogenous patient populations may enable smaller sample sizes, the increased eligibility criteria may also increase recruitment challenges or make it harder to find the “right” patients for inclusion. In some allergy studies, for instance, biomarker use is expected to lead to smaller and more intensive trials. While it is difficult to predict the impact that precision medicines will have on eligibility criteria or trial duration, experts explain oncology and rare disease trials will be

similarly affected, along with cardiovascular, endocrine and respiratory trials, which will see an increase in criteria. In oncology, biomarkers are helping to define tumor subsets for recruitment, shifting approaches from tissue of origin or histologically-defined tumor indications to genetically defined indications.

SLOW APPROVAL FOR DRUGS WITH COMPANION DIAGNOSTICS

In oncology, for drugs assessing novel biomarkers, it may be necessary to create a companion diagnostic. Regulatory rules to develop companion diagnostics may make drug approval more difficult.

ADD A NEW DIMENSION OF GENOMIC DATA ACCESS TO TRIAL RECRUITMENT

Many current investigational oncology trials now include exploratory or investigational biomarkers, necessitating coordination with molecular profiling companies that have access to next generation sequencing and other biomarker data to support patient recruitment. The results of these molecular profiling tests are not necessarily available in electronic medical records, so stakeholders must partner with multiple molecular profiling companies to identify the right patients for targeted therapy trials that require prospective identification of a specific biomarker for study entry. Trial sponsors must therefore partner with companies that curate molecular profiling data to identify sites with relevant patients.

STRENGTHEN DRUG EFFICACY SIGNALS AND REDUCE SIDE EFFECTS

Patients selected for predictive biomarkers in the enrollment process will help to enroll the right patient groups and reduce the likelihood that efficacy signals will be cloaked by less responsive or inappropriate patients. This will help reduce risks of trial failure, especially in

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NASH, allergy and cardiovascular trials. In cardiovascular trials, they can identify high-risk individuals, as well as likely-responders, enriching study populations, increasing event rates and increasing the probability of trial success. In Phase II and III infectious disease and vaccine trials, they can be used to identify a population at risk of disease or severe or prolonged infection, and therefore focus trials subjects to those in the most need of a new therapy. In infectious diseases, biomarkers can also predict patient response to antimicrobials, which may rely on the subject's immune response for best eradication of a pathogen, and are shifting therapies to align to patient-specific response. For oncology, biomarkers may help predict responders and non-responders to immuno-oncology therapies.

ENABLE NOVEL TRIALS DESIGNS INCLUDING BASKET TRIAL DESIGNS

As with patient stratification for clinical trials, the continued adoption of predictive biomarkers in clinical trials will also lead to different trial designs. Experts explain oncology trials will change from histology-driven to biomarkers-driven, leading to smaller sample sizes and an increase in basket trials - those trials that measure the effect of one drug on a single mutation across a variety of tumor types. For autoimmune trials, biomarkers will enable novel and adaptive trial designs, potentially leading to more success and resulting in more precision medicines.

ENABLE A SHIFT TO MORE STANDARDIZED EFFICACY AND SAFETY ENDPOINTS AMONG BIOMARKERS RELATED TO THERAPEUTIC RESPONSE

As our understanding of molecular progression of disease grows and a tighter correlation of some molecular biomarkers with clinical endpoints and disease outcomes is demonstrated, some biomarkers will begin to gain importance as measurable trial endpoints themselves. These biomarkers of therapeutic response, though not used to stratify patients by

disease susceptibility, can be considered an accepted indicator of future clinical outcome. In some cases, this will enable shorter trial durations. In early-phase neurology trials and in rare diseases, for instance, trial success and outcomes will increasingly be assessed based on surrogate biomarkers. Overall, standardized biomarker endpoints will be sought as substitute endpoints when the current clinical assessments are poorly measurable or have long time-horizons, or where trial sizes or current trial costs are onerous. For instance, there is a great deal of interest in finding biomarkers for diseases, such as RSV, to inform development without the need for 10–20,000 patient trials. In allergy trials, if a valid biomarker for response to a food allergy treatment were found, it would be able to reduce the number of food challenges - an expensive and risky procedure - thus improving both patient safety and cost. In reproductive health, the possibility of biomarkers in endometriosis, preterm labor or preterm birth and chronic bladder pain would similarly transform both patient care and therapeutic trials. Overall, in situations like these where a biomarker can substitute for a difficult or ambiguous clinical endpoint, these trials will see the greatest benefit, yielding large savings in terms of patient numbers, time and likelihood of success.

CHALLENGES

It is difficult to predict the impact of biomarkers on trial duration. While study timelines may decrease due to a higher predicted treatment effect, recruiting narrower patient populations may extend timelines. Additionally, biomarkers will not be effective in trials unless they correlate well with clinical endpoints. For this reason, biomarker performance will likely be tested in a Phase I setting and only used for testing efficacy in later phases. In vaccines, although antibodies can be measured as biomarker endpoints in some cases, it is expected large clinical endpoint trials will remain necessary for other vaccines where these endpoints are not predictive of efficacy.

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Changes in the Regulatory Landscape

Recent legislation and guidelines, such as 21st Century Cures Act, the EMA's adaptive pathways approach, the FDA guidance document 21 CFR Part 11 and the EMA's Clinical Trials Regulation, are influencing clinical development. The 21st Century Cures Act provides for a number of regulatory changes in the United States by promoting acceptance of more diverse drug development approaches, including: novel designs (e.g., adaptive trials), risk-based monitoring, RWD use within trial, use of digital health technologies, electronic records and electronic signatures in trials and biomarkers and precision medicine approaches.²¹ Separately, the European Union Clinical Trials Regulation aims to standardize trial submissions and data reporting in the European Union to create a favorable environment to conduct clinical trials and improve trial efficiency.²²

Changes in the regulatory landscape are influencing clinical development, and are expected to:

ALLOW FOR NOVEL TRIAL DESIGN AND ENDPOINTS

Adaptive trial designs have the potential to reduce development time and control trial costs. Guidance for adaptive trials designs have been put forth by both the FDA and the EMA,^{23,24} and other legislation is also broadening the view on acceptable trial designs. Autoimmune, oncology, neurology and gastrointestinal trials will benefit from adaptive trials, virtual trials (e.g., telemedicine) and novel endpoints. Experts continue to believe changes in the regulatory landscape are necessary to allow for more efficient and targeted clinical trial designs. This is particularly true for rare diseases, vaccines, and rare infectious diseases, and allowing for more adaptive trials can reduce vaccine trial costs and timelines. In infectious disease, thought leaders expect increased acceptance by regulators of additional infection challenge models that can be used in Phase I studies. Experts in oncology note regulators

in both the United States and Europe are amenable to new drug development approaches, including risk-based monitoring, which is recommended by the FDA. Regulators may also permit the use of mobile and wearable technology for oncology trials, as well as electronic records and electronic signatures. These regulatory initiatives are most applicable when the manufacturer is pursuing an indication with an unmet medical need, regardless of phase.

INCREASE THE LIKLIHOOD OF APPROVAL BY PROMOTING USE OF BIOMARKERS AND OTHER TECHNOLOGIES

The 21st Century Cures act provides funding for the Precision Medicine Initiative, as well as a framework that supports the development and incorporation of biomarkers. As the use of biomarkers grow, experts in allergy, oncology and neurology expect them to have an impact on regulatory approval. The use of novel biomarkers as surrogate endpoints of treatment outcomes will also grow as part of infection treatment trials. Experts additionally note evolving regulations will allow for more options in disease-modifying trials, which are typically dependent on either predictive or surrogate biomarkers, in therapy areas such as neurology and allergy.

HELP ACCELERATE DRUG DEVELOPMENT

By decreasing regulatory requirements for standard data types to prove a drug's safety and efficacy, experts believe drug development will accelerate in the cardiovascular space. However, thought leaders caution this needs to be done carefully so the quality of the trials that are conducted using novel designs are high, and the challenge will be to ensure these studies are rigorous and provide robust results. Respiratory thought leaders also note they expect faster submissions and faster feedback from regulatory agencies. Regulatory

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changes providing for multi-sponsor trials could make trials in the rare disease space more feasible. The FDA and EMA have already allowed a variety of different designs in ultra-rare diseases and continuing that theme would speed development, especially in ultra-rare areas. In pediatric oncology, regulatory changes will mandate more trials based on drug mechanism of action rather than tumor type. GI/NASH experts expect new regulatory options would increase trial success and reduce trial complexity.

DIVERSIFY TRIAL INCLUSION TO INCLUDE ADDITIONAL POPULATIONS

Oncology experts say recent changes in China CFDA will dramatically increase oncology trials that include China as a site, improving the diversity of patients overall in oncology trials. For infectious disease and reproductive health, regulatory agencies are expected to compel sponsors to ensure more diverse and at-risk populations are included in trials, for example by using adaptive trial designs. These at-risk populations include low- and middle-income, hard to reach populations and vulnerable age groups, such as neonates and premature babies at highest risk of age-specific severe infection. However, some experts caution this trend may not make the clinical development process more efficient.

PROMOTE THE UPTAKE OF RWD AND RWE IN CLINICAL TRIAL DESIGN

While randomized controlled trials remain the gold standard for evidence in regulatory submissions, there has been increasing acceptance of the use of RWE and RWD by regulators at both the FDA and EMA. According to infectious disease experts, regulatory agencies could drive use of national pregnancy registries as historical comparators for immunization and treatment trials in pregnancy. The availability of RWD for use as comparator arms or to provide evidence of safety or efficacy will also be particularly valuable in late-stage oncology trials. Furthermore, support from regulatory agencies may allow for earlier approval of vaccines using RWD post-approval studies that track long-term safety. This would be particularly helpful when epidemics occur and a vaccine is needed quickly, such as with the recent Ebola outbreaks.

CHALLENGES

In these changing areas, regulatory agencies have been careful to ensure the quality of the trials that are conducted using novel designs are high. This will be an ongoing process with greater expertise gained along the way. Some experts in reproductive health and respiratory do not expect the changing regulatory landscape to significantly impact clinical development. Vaccine experts point out regulatory agencies currently collaborate with sponsors about optimal study design for vaccines, and so the regulatory landscape is already customized for novel or priority vaccine products.

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Availability of Pools of Pre-Screened Patients / Direct-to-Patient Recruitment

Databases of individuals who consent to make their data available for research, including 23andMe,²⁵ the Precision Medicine Initiative (PMI) Cohort Program²⁶ and databases run by companies, such as Evidation,²⁷ provide well characterized populations or pools of individuals that can be leveraged for inclusion in clinical trials. Collected data may include behavioral and lifestyle information, genetic information, digital biomarkers and medical conditions, and metadata such as age, sex and location, among others. In addition, social media, blogs and online forums, and companies, such as PatientsLikeMe,²⁸ empower patients to find clinical studies.

Pools of pre-screened patients and direct-to-patient recruitment will have a positive impact on clinical development, and are expected to:

FACILITATE RECRUITMENT AND ATTAINMENT OF PATIENT ACCRUAL TARGETS

The use of pre-screened patient pools and direct-to-patient recruitment has the potential to ensure trials do not fail due to lack of recruitment. Overall, by providing a better understanding of patient types available for clinical trial enrollment and identifying patients that match clinical trial requirements, accelerated recruitment is expected across all therapy areas, along with reduced reliance on principal investigators for success. Such pools may also reduce the waste in screening one trial at a time by enabling the screen failures from one trial to match the criteria of another trial. As the size of patient pools grow, they will increase the likelihood of finding matches, which will be useful for autoimmune and allergy trials that have difficult inclusion or exclusion criteria, along with large neurology and respiratory trials and other long-term studies. Along with biomarkers, they will also enable the creation of more homogeneous patient populations within trials that meet eligibility criteria, aiding in the

neurology space. For rare disease trials, finding patients is a critical barrier, and pre-screened patient pools and direct patient recruitment will therefore have a positive impact on recruitment for these trials. The use of pre-screened patient pools will also play a fundamental role in the future of oncology - as well as precision medicine more generally - as providers and vendors conduct more genomic and histological testing, facilitating enrollment in trials targeting these defined patient subsets. However, high-quality pools of well profiled and accessible patients are still currently lacking in oncology.

REDUCE TRIAL DURATION

The existence of pre-screened pools of patients could help reach accrual targets more efficiently, leading to a reduction in trial duration, with a potentially lower screen-failure rate. For infectious disease, this can greatly reduce the duration of studies and lead to first patient enrolled (FPI) faster. For seasonal vaccine trials, access to pre-screened pools of healthy volunteers is considered essential to completing trial recruitment in a compressed timeframe, and overall, timelines for Phase I healthy volunteer and first-in-human trials stand to benefit. In the future, the field of vaccinomics (which provides a conceptual framework for understanding and predicting immune response to vaccines)²⁹ will depend on pre-screened patient pools in the development of customized vaccines.

INCREASE PATIENT FLOW TO SITES

As patient awareness of such pools and clinical trials improve, patient flow to sites is likely to be improved. This will be critical for autoimmune and allergy trials with high screen failure rates, such as seasonal allergic rhinitis immunotherapy trials and the creation of additional pools in these therapy areas are expected.

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IMPROVE TIME TO CLINICAL TRIAL INITIATION AND ENABLE EARLY MARKET AVAILABILITY

Rapid clinical trial initiation and early market availability are expected due to increased use of pre-screened patient pools and direct-to-patient recruitment. In rare disease trials, this trend makes it easier to approach patients directly versus through traditional physician-patient interaction.

ALLOW FOR SUCCESSFUL INQUIRY INTO GENE-ENVIRONMENT INTERACTIONS

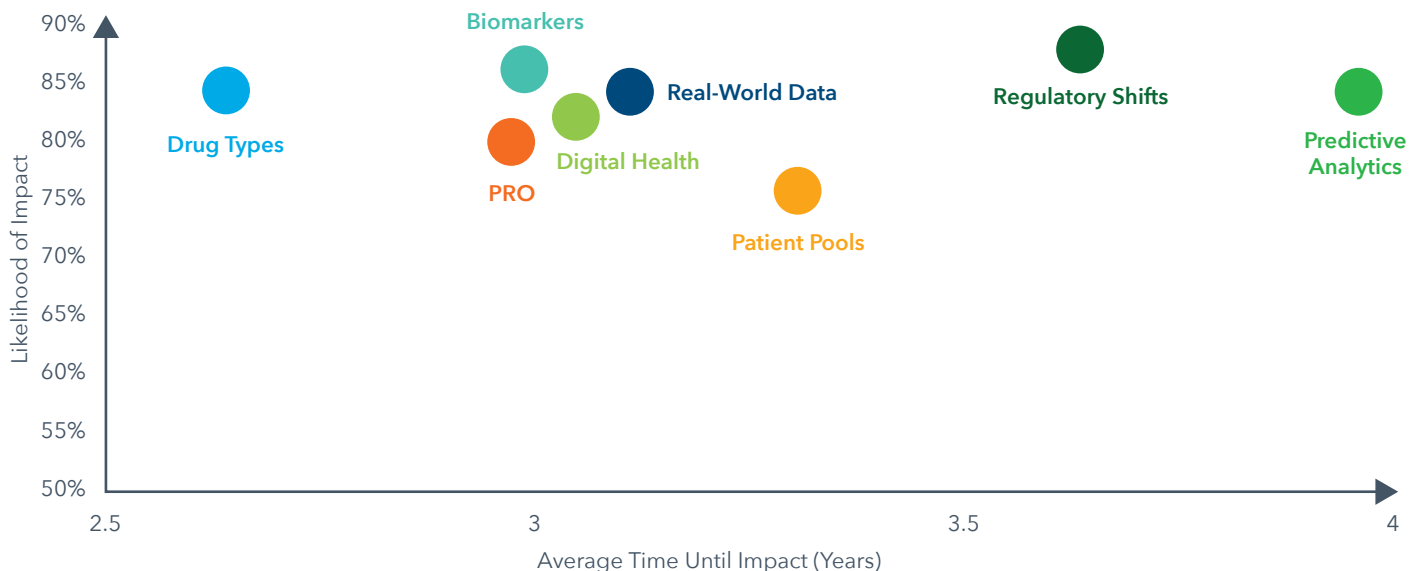
Gene-environment interactions may be more identifiable in pools of pre-screened patients and allow for investigation into “modifiable” factors of a disease, which could benefit the field of reproductive health. For example, if a new drug impacts a modifiable factor or process, then efficacy in the patient subgroup will be more likely.

CHALLENGES

Direct-to-patient recruitment can be a complex undertaking and there is some skepticism from experts around the usefulness of currently available pools of pre-screened patients including biomarkers, demographics or prior treatment data. They feel that for patient pools to be successful, investment by these organizations and companies in proof points demonstrating their quality and usefulness are needed.

Most trends will reach their peak impact within 2.5-4.0 years and all are considered to have a high likelihood of impact

Exhibit 28: Likelihood that Trends will Impact Clinical Development Across Therapy Areas and Impact Timing



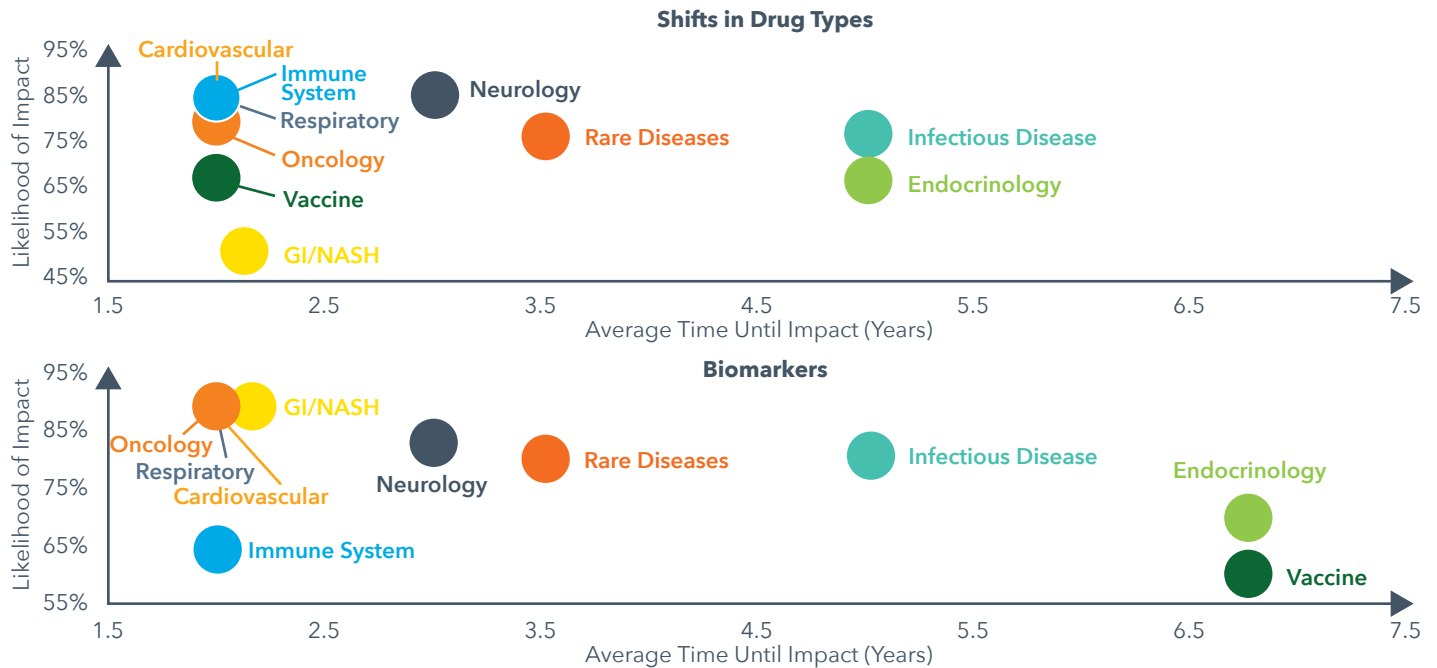
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Changes in government regulations and scientific advances – such as shifts in drugs types being tested and biomarker use – are most likely to transform clinical development.
- Shifts in drug types being tested will have an impact most immediately, while predictive analytics will take the longest to realize its full impact.
- While regulatory shifts are the most likely to have an effect on clinical development, with an 85% likelihood of impact across therapy areas, changes are also expected to impact more slowly than other trends.
- For instance, in the cardiovascular space, though regulatory changes are nearly certain (90%) to have an effect, these are expected in a 7–10 year period.
- The most immediate effect of regulatory changes is expected to be in the respiratory space, followed by neurology and oncology.
- Pools of pre-screened patients was deemed the least likely to have an impact overall.
- Respiratory and vaccine trials, however, will be particularly affected by pools of pre-screened patients in the near term, followed by rare disease, endocrinology and infectious disease.

Chart notes: Trends are weighted by the nine therapy areas considered in our analysis. Rare disease overlays multiple therapy areas and is therefore excluded from this weighting.

Changes in scientific advances will impact clinical development across most therapy areas in the near term

Exhibit 29: Trend Likelihood of Impact and Timing by Therapy Area



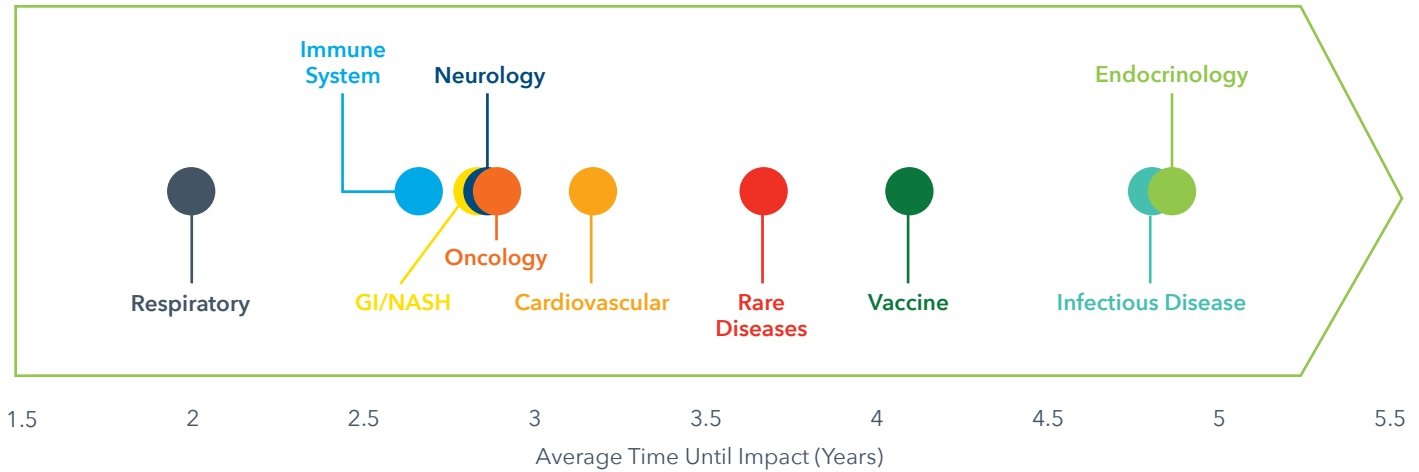
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Both the shifts occurring in drugs types under development and biomarker use are expected to impact 5+ therapy areas within 2.5 years.
- Shifts in drug types are most likely to impact cardiovascular, immune system, respiratory, oncology and neurology trials in the short term, as disease-modifying therapies, biologics and new mechanisms of actions, are the major drivers. In therapy areas like gastrointestinal trials, experts say shifts have already taken place.
- Infectious disease and endocrinology trials will be impacted more slowly by trends overall, including scientific advances, with little impact to productivity in either of these areas.

Chart notes: Therapy areas show the average impact across all trends.

Many of the therapy areas with the most complex trials will see impacts of these trends within 3 years

Exhibit 30: Trend Timing by Therapy Area in Years



Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- At a therapy area level, GI/NASH, neurology and cardiovascular trials were also deemed most likely to see changes over the next several years, with early changes resulting from nearly all trends (excluding pools of pre-screened patients for neurology and cardiovascular in 4-5 years and regulatory in cardiovascular at 8 years).
- Infectious disease and endocrinology trials will be impacted more slowly by trends.
- The trends most likely to affect GI/NASH are biomarkers and a shift towards use of PRO data.
- While endocrinology is less likely to be affected by trends and trends will impact more slowly, among these, pools of pre-screened patients, real-world data and regulatory shifts are the most likely to impact (80%) and will reach their peak impact in the medium term (4-6 years).
- The most stable areas of clinical development are expected to be endocrinology and reproductive health which are less likely to be affected by trends.

Chart notes: PRO = patient-reported outcomes.

Modeling future trial productivity

- Results of the Clinical Development Trends Impact Assessment show each of the eight trends will have a differential impact on trial productivity, success and effort across therapy areas in the next five years.
- Biomarkers will have the greatest impact on clinical productivity yielding 34% average increases across therapy areas and trial phases and the greatest increases in success rates of 27%.
- Pools of pre-screened patients will yield a similarly high increase in productivity of 29% on average by driving the largest average declines in effort of -11%.
- Shifts in drug types and the incorporation of PRO into trials are expected to increase trial effort by 4% and 2%, respectively, on average across all trials and therapy areas, and will decrease productivity in 4-5 therapy areas.
- In oncology, pools of pre-screened patients that will accelerate trial recruitment and biomarkers that will improve success rates will yield productivity improvements as high as 104% and 71%, respectively.
- Biomarkers will also yield consistently high improvements of over 45% across four other therapy areas: GI/NASH, rare disease, neurology and cardiovascular.
- Oncology and neurology trials will see approximately 30% or greater improvements in productivity over the next five years - the largest increases in productivity across therapy areas - while respiratory will see the largest decrease in productivity.
- Along with biomarkers, neurology trials will see the most significant impact from regulatory changes and digital health.
- Respiratory trials will only see positive productivity effects from real-world data and predictive analytics – both derived from the growth in the use of big data and its analysis.
- While trends vary in their impact on productivity across phases, the most significant productivity changes will occur in Phase II trials.

Modeling the Impact of Key Trends on Clinical Trial Productivity

A productivity index

The productivity of the clinical development process can be considered as a measure of trial outputs (e.g., 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.). To obtain current-state measures of success, complexity and trial duration, trial complexity attributes were leveraged from Cortellis clinical trial database (mean number of endpoints, sites, countries, patients, eligibility criteria), as well as data on trial duration, and success metrics calculated from IQVIA™ Pipeline Intelligence (see Methodology).

Modeling the impact of trends on productivity

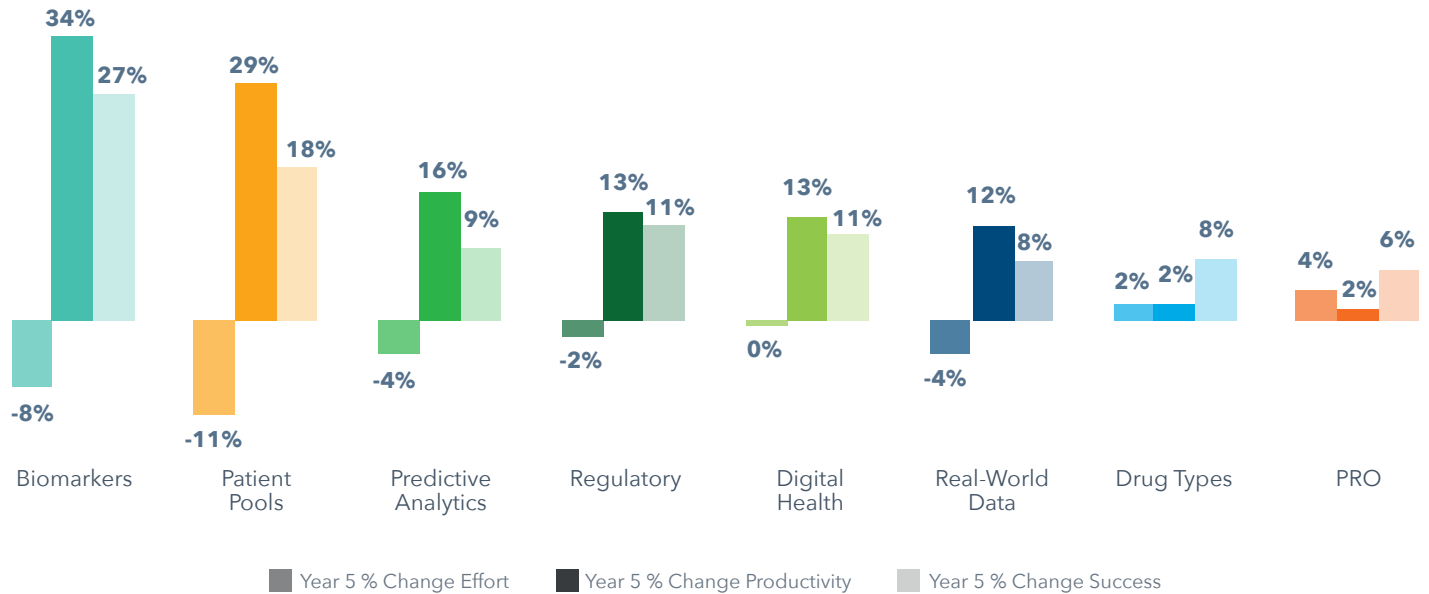
To model the magnitude of impact on clinical development productivity that can be expected due to the eight key market trends, responses from IQVIA experts to the Institute Clinical Development Trends Impact Assessment (see Chapter 4, Drivers of change in clinical development) were leveraged. Because the assessment tool was designed to predict the impact quantitatively on each element of productivity in the index (measures of complexity, success and duration), this enabled us to forecast changes due each trend per therapy area. Additionally, predicted timings of changes provided the basis for modeling the overall impact per phase across a 10-year period relative to historical data. Impact factors based on predicted impact were applied to recent average metrics - the average of 2016–2018 values - based on survey responses. Increases in these values were projected to future years 1–10 based on S-curves, which is in-line with market adoption patterns, and based on predicting timings and assumptions when saturation, hyper-growth and takeover would occur.²⁶

Estimating the collective impact of changes on clinical development productivity

Because expert predictions and associated modeling were performed for each trend at the therapy area level - absent an assessment how each trend might influence the other - combining the impact of trends poses challenges. While averaging the impacts of these changes would be an understatement of effect and allow trends with little effect to damp down the effect of other with major impact, summing the impact of trends is likely an overstatement and may result in unrealistic values. In this section, where total impacts of all trends are presented, the former, more conservative, approach of averaging the impact of trends is used - except where otherwise noted - and should be considered in this context.

Biomarkers will have the greatest impact on clinical productivity yielding a 34% average increase across all phases of development

Exhibit 31: Predicted Percent Change in Productivity, Effort and Success from 2018 to 2023 by Trend



Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

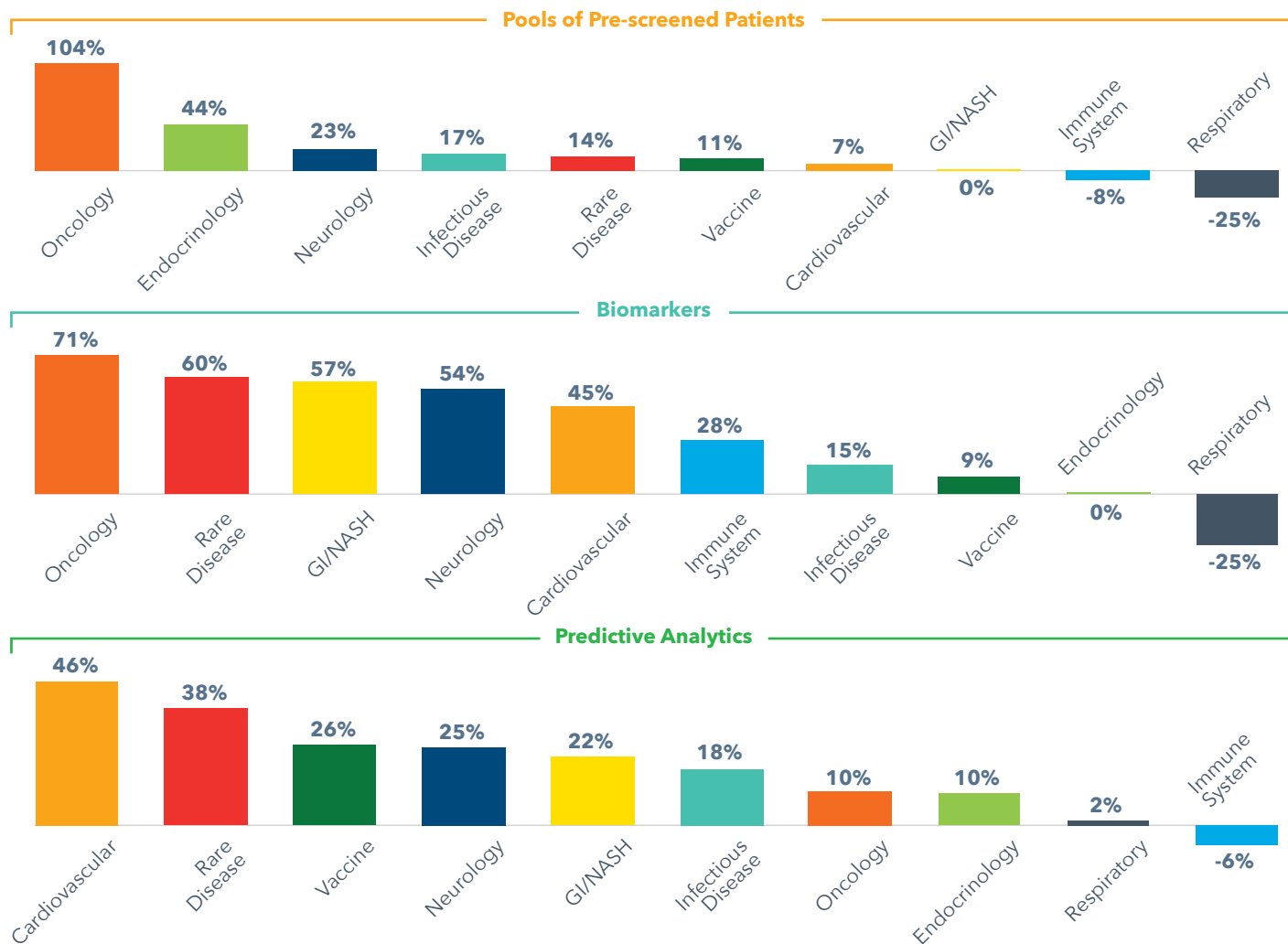
- While all trends are expected to yield improvements in trial success rates, increases in productivity will additionally be driven by decreases in trial complexity and duration (i.e., reductions in effort) from most trends.
- Only shifts in types of drugs being developed and incorporation of PRO into trials are expected to increase trial effort.
- Biomarkers and the development of pools of pre-screened patients to aid in trial recruitment are expected to have the largest positive impacts on productivity – 34% and 29% respectively – on average across all therapy areas.
- Pools of pre-screened patients will have the second greatest impact, with a 17% increase in productivity – the result of the largest percentage drop in effort (-12%) and an 18% increase in success.
- While predictive analytics and PRO are among the trends that will yield the smallest benefit to success on average across all therapy areas, in respiratory these were both predicted to yield large increases to success and largest increases in effort.
- The collective impact of all trends on productivity can range as high as 119% (impact summed), or as low as 15% (impact averaged), depending how effects of these eight trends overlap/synergize. Trial effort is likely to decrease by 3–23% and success is likely to increase 12–98%.

Chart notes: PRO = patient-reported outcomes. Displays the percent improvement in these values over 2016–2018 average values across all phases and the nine therapy areas included in the analysis. Values were weighted by the number of trials per therapy area and by phase. A productivity factor of 97.61 was added to the index numerator, and multiplied with success, to allow historical (2010–2018) productivity values to stretch between a min of 0 and max of 100. Exhibit displays the weight-averaged impact across all trial phases.

MODELING FUTURE TRIAL PRODUCTIVITY

Pools of pre-screened patients and biomarkers will yield productivity improvements as high as 104% and 71%, respectively, in oncology

Exhibit 32: Predicted Percent Change in Productivity per Trend by Therapy Area from 2018 to 2023



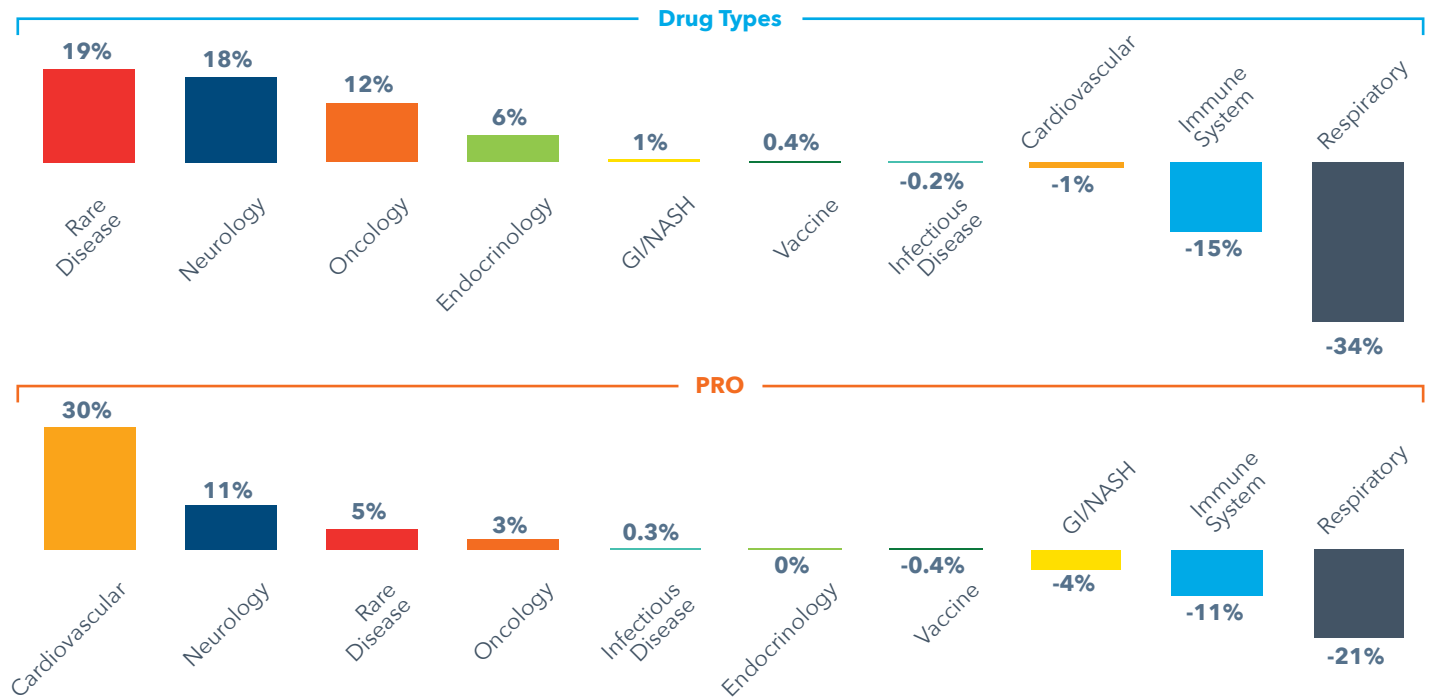
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Outside of oncology, biomarkers are additionally expected to yield consistently high productivity improvements of over 45% across four therapy areas: GI/NASH, rare disease, neurology, and cardiovascular.
- The impact of biomarkers and pools of patients on respiratory trial productivity is negative, driven by significant increases across all aspects of complexity attributes and trial duration. This may be in part to challenges around biomarkers for some respiratory diseases, such as non-type 2 inflammatory mechanisms for asthma, difficulties interpreting biomarker results for COPD, and challenges around patient recruitment.^{23,24,25}
- Predictive analytics is expected to have significant positive impact on productivity in all therapy areas excepting immune system disorders, which include allergy, immunology and rheumatology trials.

Chart notes: Displays the percent improvement in productivity values over 2016–2018 average productivity values across all phases and the eight trends included in the analysis. Absolute values were weighted by the number of trials per phase. Exhibit displays the weight-averaged impact across all trial phases. Rare disease category represents rare diseases across therapy areas and therefore is not mutually exclusive with the other nine therapy areas analyzed.

Shifts in drug types and PRO are both expected to decrease productivity in 4-5 therapy areas

Exhibit 33: Predicted Percent Change in Productivity per Trend by Therapy Area from 2018 to 2023



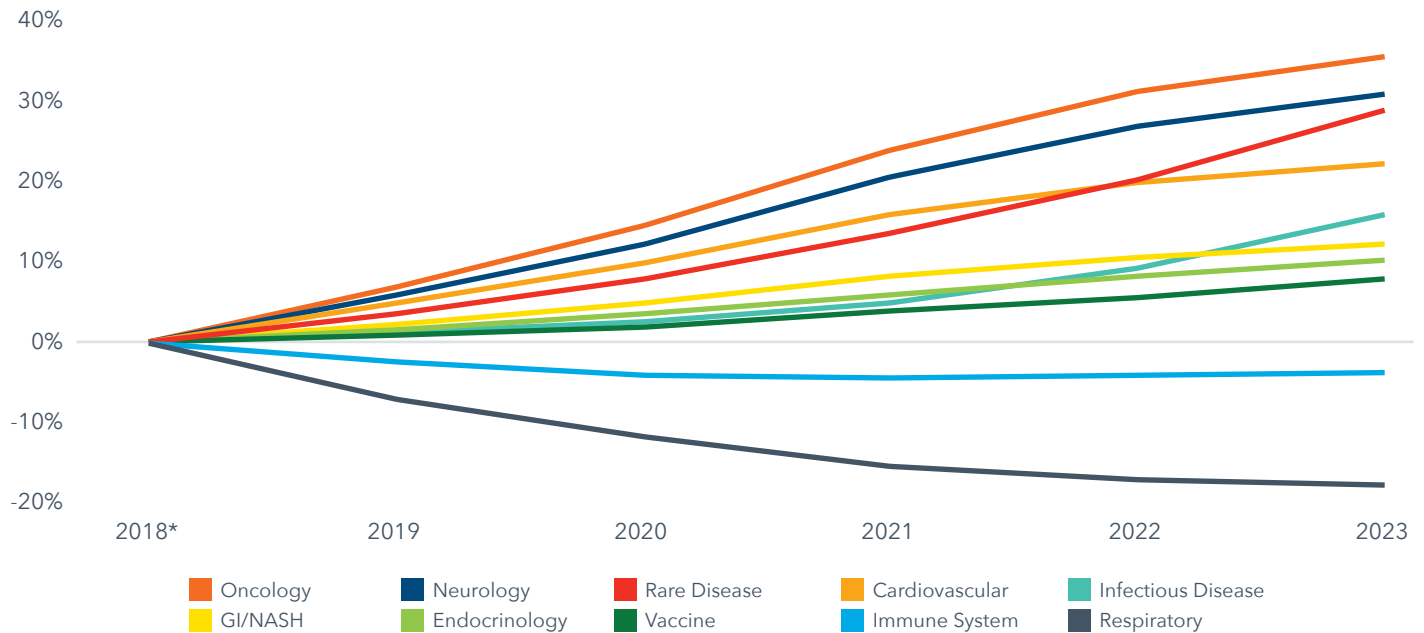
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- As a driver of trial complexity, shifts in drug types under development are expected to increase trial effort across all therapy areas except neurology and oncology, in part because novel drug types such as RNAi therapies, disease-modifying therapies and biologics are already available.
- Increased or neutral impacts on success rates are also expected across all therapy areas due to shifts in drug types.
- For all areas where productivity is declining due to shifts in drug types, increases in trial complexity or duration outweigh the positive effects of increased success.
- Inclusion of PRO in clinical trials is expected to be a main driver of effort, increasing it by 4% on average across all trials and therapy areas, and by as much as 20 and 60% for respiratory and immune system trials, respectively, and resulting in -11% and -21% decreases in productivity, respectively.
- PRO is only expected to reduce trial effort in cardiovascular and neurology trials by -16% and -3%, respectively. In cardiovascular trials, experts explain that PRO will lead to a reduction in trial duration, as switching away from survival and other standard endpoints leads to faster trial completion.
- Nonetheless, these effects on productivity will be offset by expected increases in success for all TAs except for GI/NASH, possibly because PRO is already a part of some GI clinical practice and trial execution for indications such as irritable bowel syndrome.²⁷

Chart notes: PRO = patient-reported outcomes. Chart displays the percent improvement in productivity over 2016–2018 average productivity values across all phases and the eight trends included in the analysis. Absolute values were weighted by the number of trials per phase. Zero impacts on success were expected by drug types only in vaccines and reproductive health. Zero impacts on success were expected by PRO only in vaccines and negative impacts in GI/NASH. Exhibit displays the weight-averaged impact across all trial phases. Rare disease category represents rare diseases across therapy areas and therefore is not mutually exclusive with the other nine therapy areas analyzed.

Oncology and neurology trials will see approximately 30% or greater improvements in productivity over the next five years

Exhibit 34: Average Percent Change in Productivity per Therapy Area from 2018 to 2023 as a Result of Trends



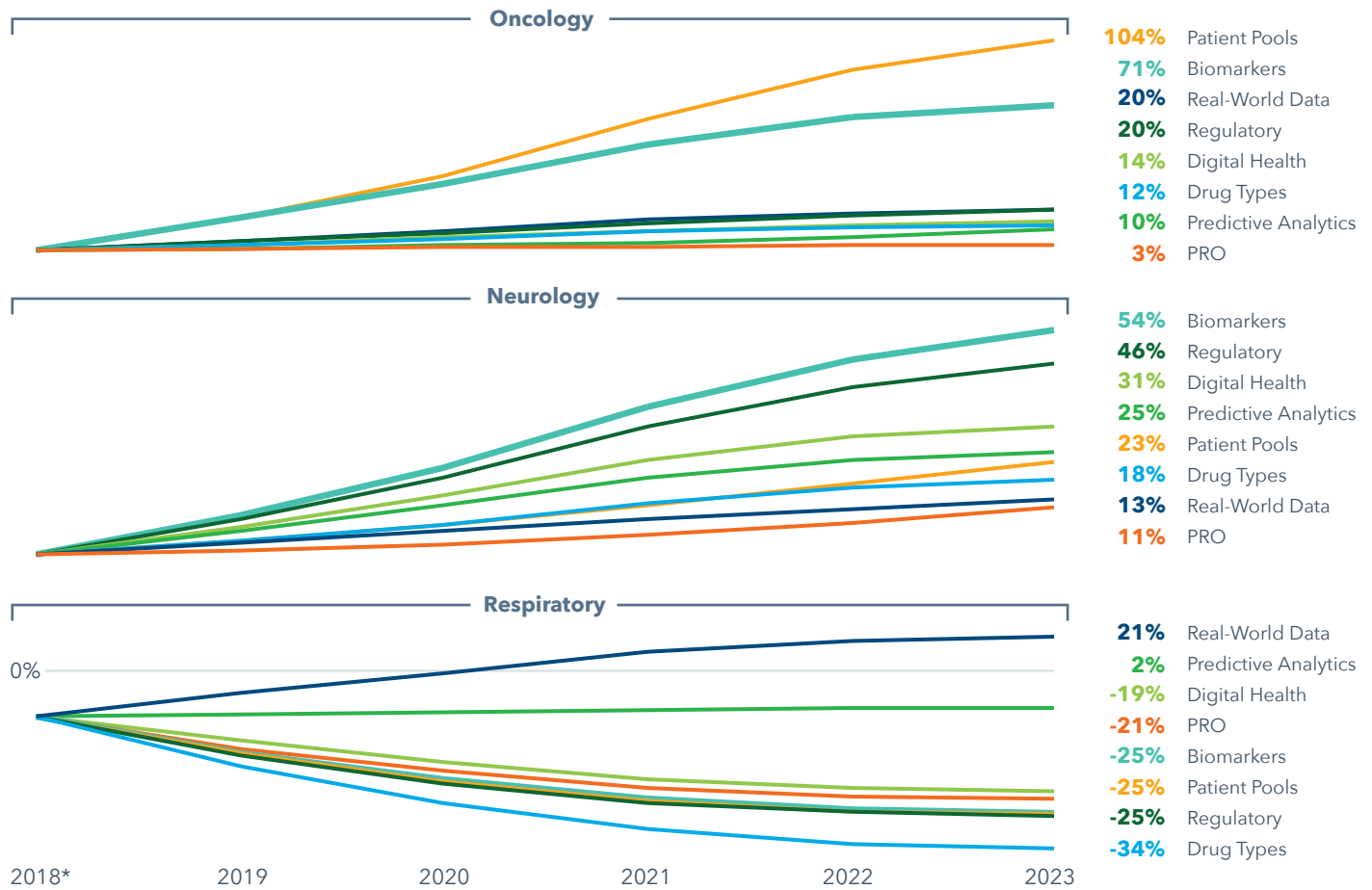
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Oncology, neurology, rare disease and cardiovascular trials will see the most significant increases in productivity on a percent basis over the next five years.
- Oncology will see the largest percentage increase in productivity of any therapy area, while both respiratory and immune system trials will see decreases in productivity.
- Infectious disease and endocrinology are also predicted to be among the top five in terms of absolute impact to productivity, however, their starting productivity values are higher.

Chart notes: *2018 indicates the year of data input for modeling, which was the average value 2016–2018. Chart displays the average effect of all trends and is therefore a likely understatement of their combined effect. Rare disease category represents rare diseases across therapy areas and therefore is not mutually exclusive with the other nine therapy areas analyzed.

Oncology and neurology will see productivity increases from all trends, while respiratory will only benefit from new uses of data

Exhibit 35: Predicted Percent Change in Productivity by Therapy Area and Trend from 2018 to 2023



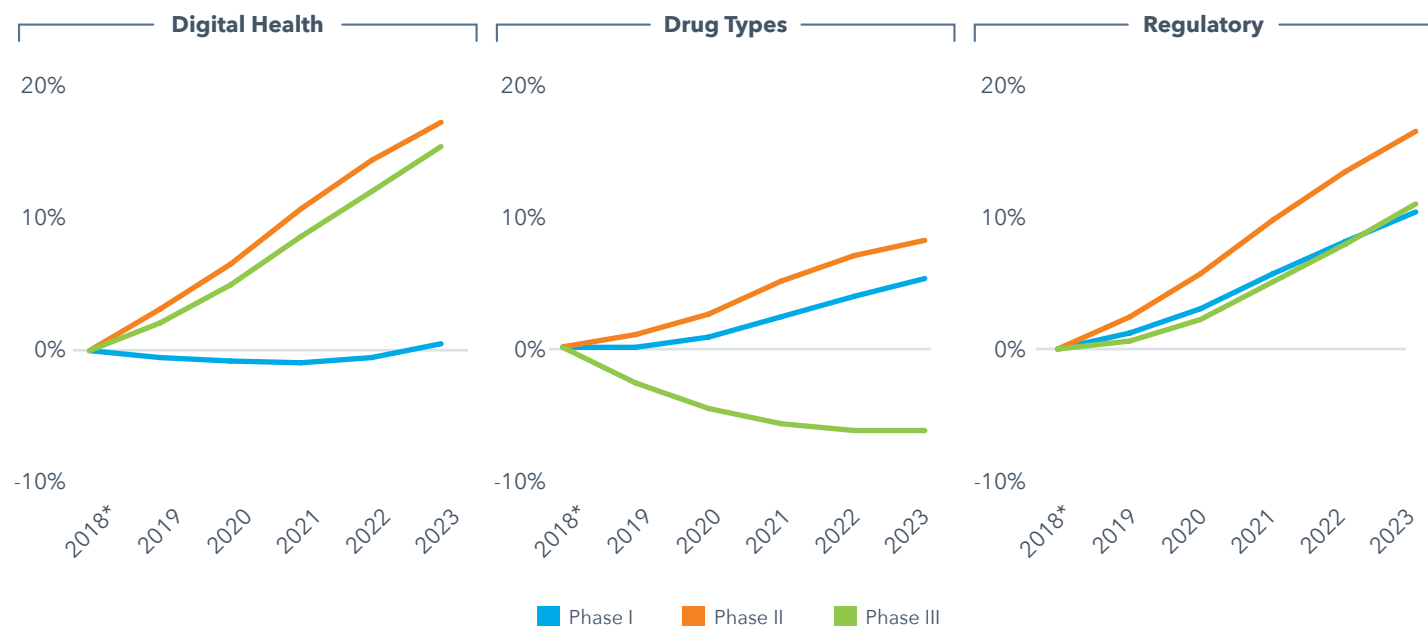
Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Oncology will be transformed by the development of patient pools that will accelerate trial recruitment and biomarkers, which will improve success rates.
- Neurology trials will see the most significant impact from digital health, followed by biomarkers and regulatory changes.
- Respiratory will only see positive effects from RWD and predictive analytics - both derived from the growth in the use of big data and its analysis - but is otherwise seeing declines.

Chart notes: *2018 indicates the year of data input for modeling, which was the average value 2016–2018.

While trends vary in their impact on productivity across phases, the most significant productivity changes will occur in Phase II trials

Exhibit 36: Predicted Percent Change in Productivity from 2018 to 2023 by Phase



Source: IQVIA Institute, Mar 2019; Clinical Development Trends Impact Assessment, Jun-Jul 2018

- Phase I trials will see the least change in productivity, with most trends yielding a modest 4–10% increase in productivity.
- Many trends in Phase I are expected to have zero impact on specific elements of complexity, effort or success.
- Digital health trends, while having 14 and 16% impacts across therapy areas in Phase II and III, will have virtually no effect on Phase I trials.
- While both Phase II and III trials will be significantly impacted by most trends, not all trends yield positive changes.
- Changes in the drug types being tested will decrease Phase III productivity by -6%, likely due to the fact that disease-modification trials and the use of NGB which may need longer-term monitoring for safety will lengthen trials most in this phase.
- While regulatory changes will have a 10–16% impact across phases, this effect will be highest in Phase II trials likely due to recent regulatory efforts to accelerate approvals on innovative therapies and some Phase II trials now being considered for registration, particularly in oncology and infectious disease.
- PRO will have little-to-no effect on average across all trial phases.
- Predictive analytics will have its greatest impact in Phase III, with a 20% increase in productivity.

Chart notes: *2018 indicates the year of data input for modeling, which was the average value 2016–2018. Exhibit shows the average values across all therapy areas.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

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

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

IQVIA MIDAS™ is a unique data platform for assessing worldwide healthcare markets. It integrates IQVIA national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and providing estimated product volumes, trends and market share through retail and non-retail channels. MIDAS data is updated monthly and retains 12 years of history.

Methodology

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 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, 25,334 distinct drugs were examined, for 126,670 potential phase transitions for events from 1977 to present. We then limited to products where the phase transitions completed between 2010 and 2018, with valid information regarding phase transitions, either successful or failed, which includes 6,815 distinct drugs and 10,009 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.

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 that have higher phase entries but dates are in the past. This can be an artifact of a drug with multiple indications with incomplete information for some of the indications in the source database.
- Drugs that 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 at indication level.

CUMULATIVE PHASE DURATIONS

Each phase success rate includes a calculation of phase duration for the records included. Durations can be calculated for success and failure outcomes and overall.

Records deemed failures due to inactivity, are measured as phase start to last active record date (LAR).

Definitions

Immune System Disorders – Includes Allergy, Immunology and Rheumatology (AIR)

ALK – anaplastic lymphoma kinase

ALL – acute lymphocytic leukemia

AML – acute myeloid leukemia

CGRP – calcitonin gene-related peptide

CLL – chronic lymphocytic leukemia

EGFR – epidermal growth factor receptor

GI –gastrointestinal

IDO –indoleamine-pyrrole 2,3-dioxygenase

NSCLC – non-small cell lung cancer

NTRK – neurotrophin receptors

PD-L1 – programmed death-ligand 1

PFS – progression free survival

NASH – non-alcoholic steatohepatitis

Emerging biopharma (EBP) companies – have less than \$500 million in annual global revenue on audited basis from IQVIA MIDAS or less than \$200 million in R&D spending in latest year.

Large pharma companies – those with more than \$10 billion annual global revenue on audited basis from IQVIA MIDAS

Next-Generation Biotherapeutics (NGB) – defined as cell, gene and nucleotide therapies

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 in 2018 regardless of the timing of FDA approval.

Orphans in this report are 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.

Biologics are defined by IQVIA as clearly identifiable molecules of biologic origin, including but not limited to products created with recombinant DNA technology and without necessarily adhering to classifications by regulatory bodies that are sometimes inconsistent with this approach.

Nucleic acid therapeutics are based on nucleic acids and include, but are not limited to antisense oligonucleotides, gene therapies, aptamers, microRNAs and RNAis. These drugs can be considered in cases where specific inhibition or replacement of a gene or RNA will beneficially alter protein expression.

References

1. KPMG Enterprise. Venture Pulse 2016. Global Analysis of Venture Funding. 2017 Jan 12. Available from: <https://assets.kpmg/content/dam/kpmg/xx/pdf/2017/01/venture-pulse-q4-2016-report.pdf>.
2. National Venture Capital Association. NCVA blog. 2019 Jan 15. Available from: <https://nvca.org/blog/8-takeaways-8-graphics-historic-2018-venture-capital/>
3. World Health Organization. Dementia Key Facts. Accessed May 2019. Available from: <https://www.who.int/news-room/fact-sheets/detail/dementia>.
4. Rare Diseases. A report on orphan drugs in the pipeline. PhRMA. 2013. Available from: http://phrma-docs.phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf
4. Rinaldi C, Wood MJA. Antisense oligonucleotides: the next frontier for treatment of neurological disorders. *Nat Rev Neurol*. 2018 Jan;14(1):9-21
6. IQVIA Institute. The Growing Value of Digital Health: Evidence and Impact on Human Health and the Healthcare System. Nov 2017. Available from: <https://www.iqvia.com/institute/reports/the-growing-value-of-digital-health>
7. Patient-Centered Outcomes Research Institute. Accessed Feb 2019. Available from: <https://www.pcori.org/>
8. Jarosławski S, Auquier P, Borissov B, Dussart C, Toumi M. Patient-reported outcome claims in European and United States orphan drug approvals. *J Mark Access Health Policy*. 2018 Nov 7;6(1):1542920
9. Gnanasakthy A, Barrett A, Evans E, D'Alessio D, Romano CD. A Review of Patient-Reported Outcomes Labeling for Oncology Drugs Approved by the FDA and the EMA (2012-2016). *Value Health*. 2019 Feb;22(2):203-209
10. Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. *Control Clin Trials* 2004; 25:535-52.
11. Applied Clinical Trials. Bharmal M, Viswanathan S. Late Phase Patient Reported Outcomes: Patient-level feedback from later studies provides a multitude of valuable answers to all stakeholders. 2009 Oct 1. Available from: <http://www.appliedclinicaltrials.com/late-phase-patient-reported-outcomes?id=&sk=&date=&pageID=2>
12. MacDougall DM, Halperin SA. Improving rates of maternal immunization: Challenges and opportunities. *Hum Vaccin Immunother*. 2016 Apr 2;12(4):857-65
13. Khozin S, Blumenthal GM, Pazdur R. Real-world Data for Clinical Evidence Generation in Oncology. *J Natl Cancer Inst*. 2017 Nov 1;109(11)
14. Kaplan AV, Baim DS, Smith JJ, Feigal DA, Simons M, Jefferys D. Medical device development: from prototype to regulatory approval. *Circulation*. 2004 Jun 29;109(25):3068-72
15. IQVIA Institute. The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch. Jan 2019. Available from: <https://www.iqvia.com/institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023>
16. RECIST. Accessed Feb 2019. Available from <http://recist.eortc.org/>
17. IQVIA Pipeline Intelligence.
18. FDA. Center for Drug Evaluation and Research. Advancing health through innovation 2018 new drug therapy approvals. Jan 2019. Available from: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf>
19. Katsila T, Spyroulias GA, Patrinos GP, Matsoukas MT. Computational approaches in target identification and drug discovery. *Comput Struct Biotechnol J*. 2016 May 7;14:177-84.

References

20. Cheng F, Zhao J, Zhao Z. Advances in computational approaches for prioritizing driver mutations and significantly mutated genes in cancer genomes. *Brief Bioinform.* 2016 Jul;17(4):642-56.
21. Congress.gov. H.R.34 - 21st Century Cures Act. 2016 Nov 25. Available from: <https://www.congress.gov/bill/114th-congress/house-bill/34/text#toc-HBC0DF02539024F65AEF0DD6A88063188>
22. European Medicines Agency. Clinical Trial Regulation. Accessed Feb 2019. Available from: <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation>
23. Wan XC, Woodruff PG. Biomarkers in Severe Asthma. *Immunol Allergy Clin North Am.* 2016 Aug;36(3):547-57.
24. Stockley RA, Halpin DMG, Celli BR, Singh D. COPD Biomarkers and their Interpretation. *Am J Respir Crit Care Med.* 2018 Dec 28.
25. Delsing L, Jauhiainen A, Brailsford W, Buxtfeldt C, Sethi T, Betts J. Finding the Patients for Respiratory Clinical Trials; Successful Recruitment by Adapting Trial Design. *Lung Dis Treat.* 2016. 2(3)
26. Mendez Juan C. Modeling market adoption in Excel with a simplified s-curve. Apr 24, 2007. Accessed August 2018. <http://web.archive.org/web/20080315071441/http://jcandkimmita.info/jc/2007/04/business/modeling-market-adoption-in-excel-with-a-simplified-s-curve/>
27. Spiegel BM. Patient-Reported Outcomes in Gastroenterology: Clinical and Research Applications. *J Neurogastroenterol Motil.* 2013 Apr;19(2):137-48

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About the IQVIA 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 IMS Institute is now the
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