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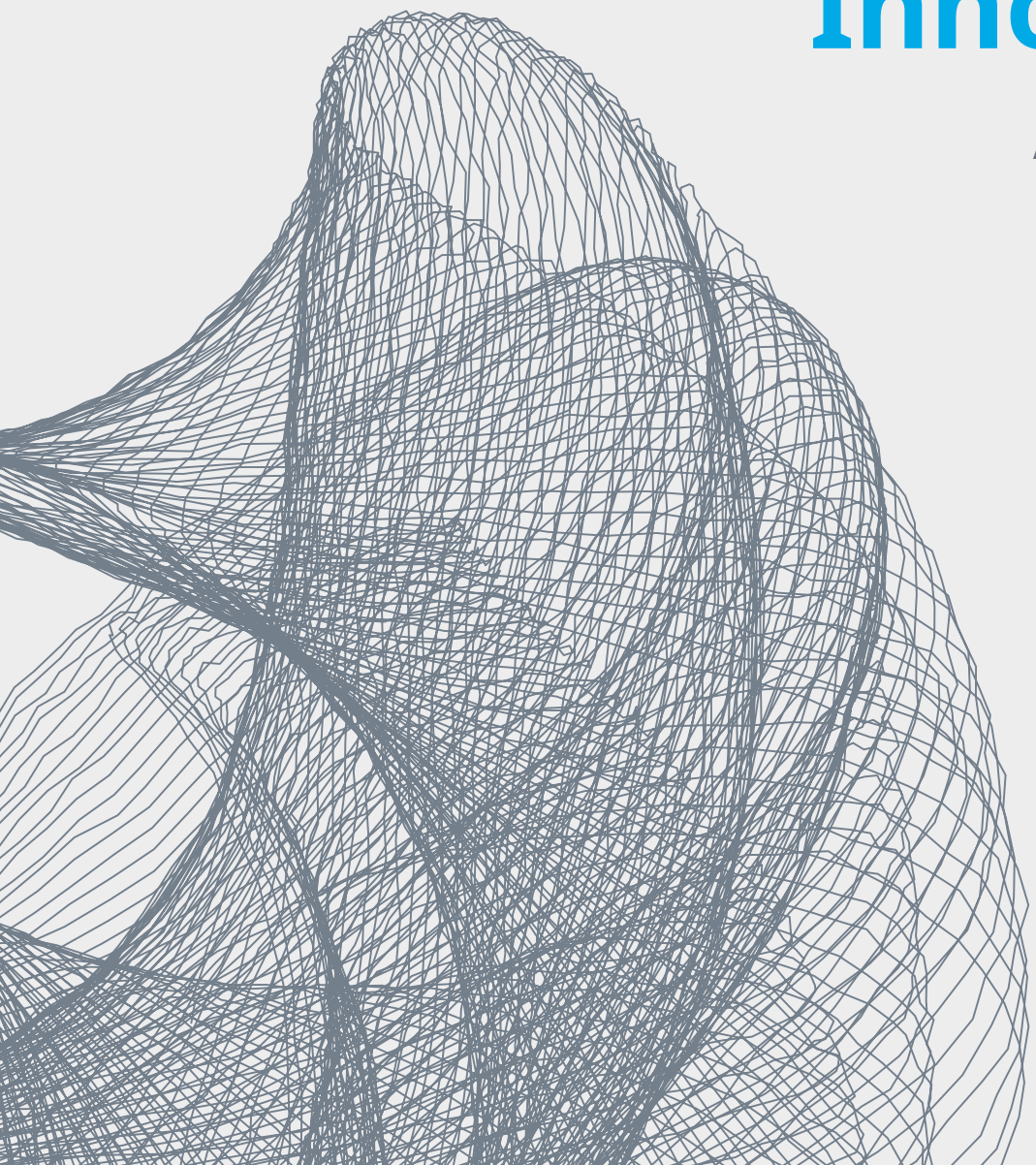
Emerging Biopharma's Contribution to Innovation

ASSESSING THE IMPACT



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2019

Introduction

The majority of biomedical innovation is developed by emerging biopharma companies, many of which have never marketed a therapy before. Over time, those companies either successfully bring their products to market or, in many cases, their assets or whole companies are acquired by others. These emerging biopharma (EBP) companies are at the root of early-stage drug development and their performance, the environment in which they operate, and their relationship to other stakeholders in the health system play a critical role in determining the future of many novel therapies and health technologies.

This report is intended to inform executives from these emerging biopharma companies (EBPs), their investors, the large pharma company executives who engage with EBPs and often purchase their assets, as well as policy-makers focused on the overall innovation ecosystem. It also has a global focus – as innovation knows no borders – and includes novel analytics and an informative segmentation of EBPs based on the commercial routes they employ to bring drugs to market, as there are a multitude of strategies being pursued in this area.

The report provides clarity on the current landscape of EBP companies and their emerging product pipelines, as well as associated clinical trial activity and levels of trial success. In addition, the report focuses on the financial deals, strategies, and organizational archetypes that lead to EBPs effectively developing and/or marketing novel products. Finally, the report provides an assessment of the overall outlook for EBPs, with a focus on how key trends will shape future achievements.

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Executive Director

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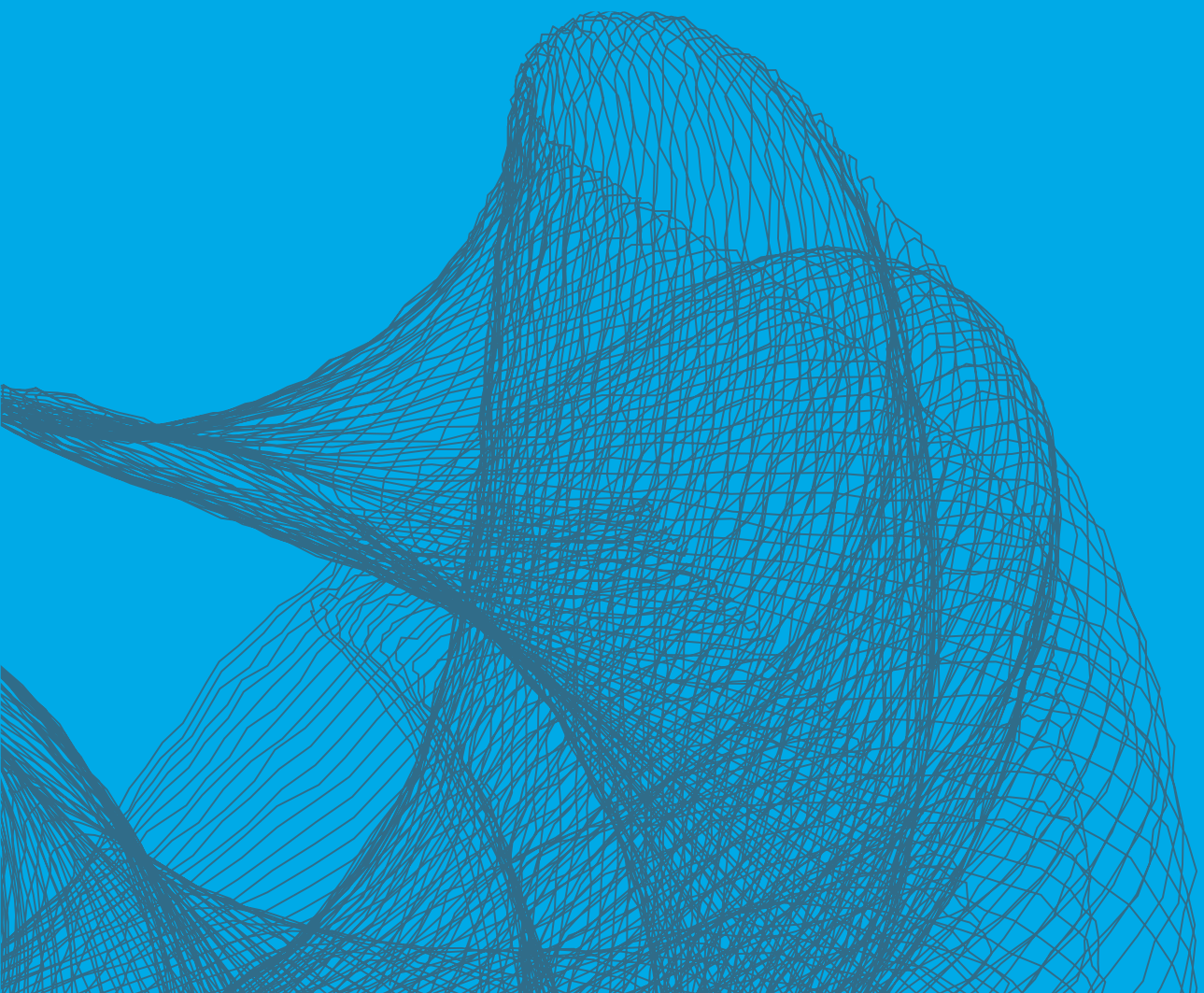


Executive summary

Emerging biopharma (EBP) is a segment of companies driving a large portion of innovation and development in the life sciences. EBP companies are defined as having less than $200 million in estimated annual spending on R&D, or under $500 million in global revenue. Emerging biopharma companies employ many strategies involving development of novel compounds, value-added medicines, and/or generics, or even license products from other larger companies for regional marketing rights. While some are not involved in R&D and may not be targets for partnering or M&A activities in the traditional sense, they do represent investment opportunities for some.

Research and development activities

There are 3,212 companies defined as emerging biopharma in 2018. Emerging biopharma companies now represent 73% of late-stage research, up from 52% in 2003, and the number of molecules under development by EBPs grew by 15% in each of the past two years. EBP companies also represent 84% of early-phase research. In total, there are 8,706 products or programs in active development, ranging from discovery to registration, with 80% from EBP companies. Oncology products developed by emerging pharma companies have increased 74% since 2013, driven by targeted agents. EBP companies are developing more than 90% of Next-Generation Biotherapeutics (NGB), which include cell, gene and RNAi technologies, among others. The top 30 emerging biopharma companies employ both traditional and cutting-edge technologies that span across therapy areas and include the most highly innovative new mechanisms in development.

EBP companies conducted 65% of all clinical trials in 2018 and are now running more trials than larger companies across all phases. Products developed by emerging biopharma companies have a composite success rate of 17% – greater than other company segments.

Commercialization performance

EBPs increasingly contribute to innovation, and these companies were the original patentees for 29 of the current top 100 drugs, which account for 40% of sales in the United States in 2018. For drugs launched in 2018, EBPs originated and launched 42% of the new drugs, a higher percentage than in past years and up from 26% in 2017. These companies have a greater focus on orphan drugs than other companies, with over half of EBP-launched drugs in 2018 receiving orphan designation and almost a quarter were approved based on a single-arm trial.

The median time for EBP companies to launch new drugs was 16.6 years in 2018, over 30% slower than other company segments. Emerging biopharma originated products generally reach the market faster if they were launched by other company segments. This may be more indicative of the value seen by the companies purchasing the assets, which was borne out in subsequent trials and faster approval, but truly understanding what drives product performance requires an assessment of how it addresses clinical unmet need and how different each product is from competing treatments. Across hundreds of launches over the ten years to 2017, EBP companies were the originators of more products in areas of high unmet need, and also those with greater product differentiation, and many of these drugs were partnered with or acquired by larger companies for launch. Of note, EBPs generally achieve lower average sales when launching new active substances than other companies.

Strategic transactions

The lifecycle of a company or a compound in biopharmaceuticals often begins with an academic research institution or a venture capital investment. Looking ahead to the innovations that will likely emerge

in the next decade and beyond, the volume of venture capital activity in life sciences offers a useful barometer of investor interest and provided research remains productive at historic levels, the output of research in the future. Venture financing has been rising in absolute terms and in the number of deals.

Collaborative deals between EBPs and larger companies have continued, and partnering deals have increasingly had payments later in the agreement with more milestones and lower up-front payments. EBPs partnering with large companies accounted for nine of the top ten partnering deals in 2018, and seven of the top ten M&A deals in 2018 involved an emerging biopharma company. There was a 78% increase in deals in 2018 when drugs were at pre-registration stage, or 62 deals compared with 36 in 2017. Large pharma continues to acquire or license assets between themselves and with EBPs, and in 2018, among 45 companies assessed, 415 deals were transacted for an aggregate disclosed value of $272 billion.

Profile of the 2008 Series A financing cohort

There were 168 startups which received series A funding in 2008, and ten years later they have achieved a variety of outcomes providing a useful benchmark on performance for startups which have received funding more recently.

Startups received funding in 2008 across a range of therapy areas, including high profile NGBs, and at varied funding levels, with half occurring in three U.S. states. The largest area of focus for these companies was oncology, mirroring its rise in importance to the overall pipeline since 2008. They also received varied initial funding levels, suggesting that some investors were seeing a proof of concept that required milestones to prove value, while others had identified a significant value and funded it to a greater extent.

Ten years after initial financing, 51% of companies were privately held and 17% had gone public. Of those 28 publicly traded companies, five now have market capitalization of over $1 billion dollars. Forty-three companies have been acquired since initial financing; more than half by other emerging biopharma companies.

Over half of financed companies have molecules in late-stage development, and six drugs from five companies were approved within ten years of financing.

Looking ahead

The environment is changing rapidly around clinical development and the marketing of drugs, and EBP companies will be operating in a highly dynamic and complicated market for the foreseeable future. Eight key trends are influencing aspects of trial design, duration and success with important implications for EBP companies. In addition, the commercial environment is increasingly under pressure related to the high level of existing healthcare spending across most economies. The companies with the greatest success in the coming years will be those that take the best advantage of three key factors: the use of data and analytics, the adoption of technology and a critical need to employ flexible business models. Some companies may choose to partner to maximize value around technology or analytics, others may make their entire focus the development of tools and approaches to sell to others. The companies that can find the best mix of these factors aligned to the assets they have in development and the capabilities they have in their organizations will find the greatest success in the coming years.

Emerging biopharma companies

It is helpful to use a set of common definitions to fully understand the role that emerging biopharma companies play in the United States and global health systems. Defining companies by revenue and pipeline activity offers a simple yet effective way of mapping types of companies.

For the purposes of this report, the following segments are discussed, and placement within those segments are determined based on the 2018 calendar year:

- Emerging biopharma (EBP) companies are defined as those with either R&D spend <$200 million or prescription sales up to $500 million. Companies with any active pipeline since 2014 were included.
- Small companies have global prescription sales between $500 million to $5 billion in the calendar year.
- Mid-size companies have global prescription sales between $5 and $10 billion in the calendar year.
- Large companies are those with global prescription sales exceeding $10 billion in the calendar year.

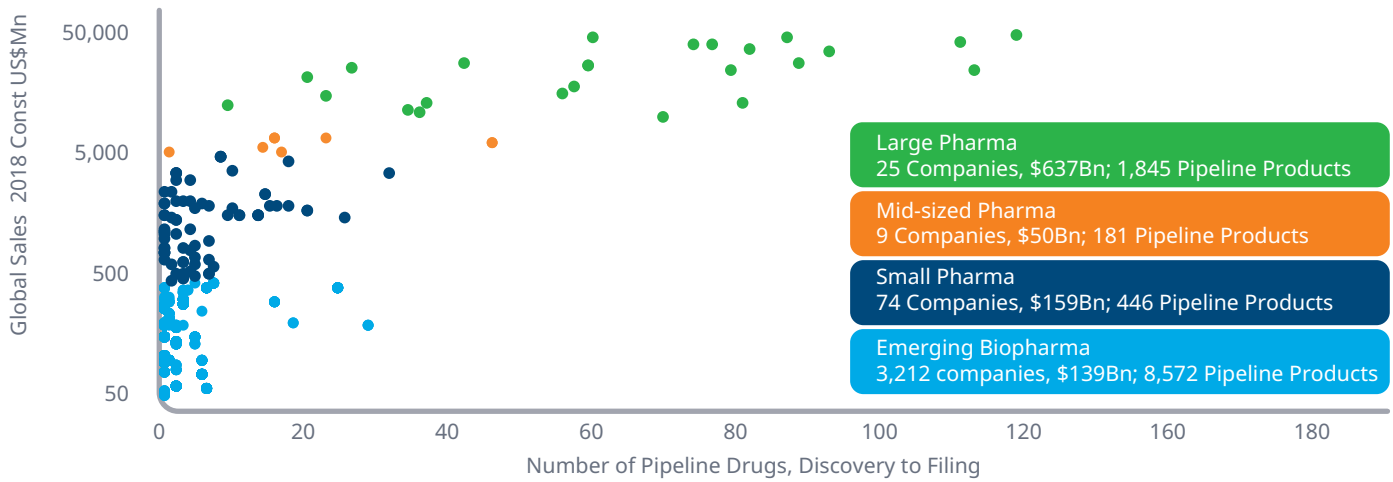
- In general, emerging biopharma companies are defined as those with $50-400 million in sales or under $200 million in R&D spending noted from public companies reporting or presence of R&D activity in the past four years if spending levels were not reported (private companies). In practice however, some companies which has less than $400 million in the past five years could have revenues up to $500 million due to high performing launch products. In this report, the sales threshold for EBP companies was extended to $500 million to maintain cohort stability over a 5-year period/time for analytical purposes.

* Note: Company segmentation has been informed by a number of sources including IQVIA MIDAS for sales revenue and IQVIA Pipeline Intelligence for R&D activity. Other sources include Clarivate Analytics Cortellis for additional information on the presence of R&D activity and EvaluatePharma for R&D spending where available (generally for public companies).

Emerging Biopharma	Sales <$500Mn, R&D Spend <$200Mn
Small Pharma	Sales $500Mn – <$5Bn
Mid-sized Pharma	Sales $5Bn – <$10Bn
Large Pharma	Sales >$10Bn

The universe of biopharma companies is diverse and includes a large set of companies defined as emerging biopharma

Exhibit 1: Global Medicine Sales and Number of R&D Pipeline Drugs per Company in 2018 by Segment



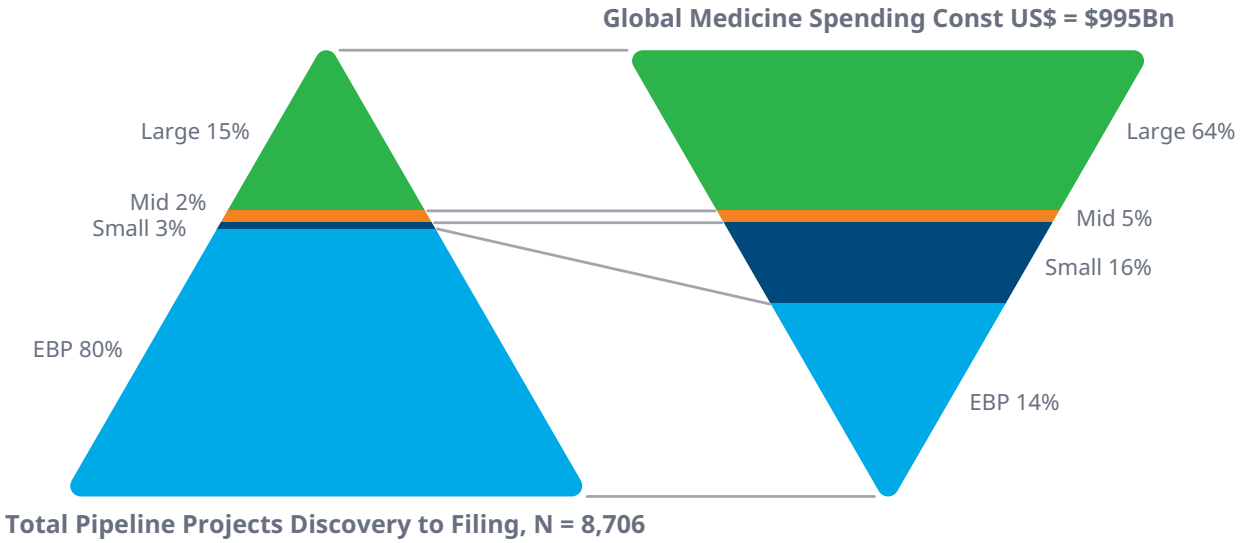
Source: IQVIA Pipeline Intelligence, Jan 2019; IQVIA MIDAS, Dec 2018

- There are 3,212 companies defined as emerging biopharma in 2018, including a subset of companies with revenues below $50 million, some of which focus on generics or are non-pharmaceutical companies acting as distributors or intermediaries in some markets.
- In this report, these smaller companies are considered emerging biopharma companies, in part because many of them have mixed strategies involving development of novel compounds, value-added medicines, as well as generics or licensing of products from other larger companies for regional marketing rights. While some are not involved in R&D and may not be targets for partnering or M&A activities in the traditional sense, they do represent investment opportunities for some.
- The number of development projects correlates directly with company size. Although EBPs are numerous, they have an average of three development projects each, while large companies average 74, and mid and small companies average 20 and six, respectively.
- The significant number of drug projects per large pharma are a reflection or the strategy of some large companies to acquire drug candidates and technologies from EBP companies.
- Some EBPs have over 20 pipeline projects, similar to their small- and mid-sized company counterparts.
- Large biopharma companies have significant research programs but oftentimes source assets from thousands of emerging firms.

Chart notes: IQVIA MIDAS revenues reported by marketing company and linked by corporation ownership but not including co-marketing or royalty payments and may understate revenues for some companies and overstate for others. Some pipeline products may be attributed to multiple companies across segments. EBPs in this chart include some smaller generic companies, distributors, parallel traders. Some others have no novel compound research but are instead focused on novel formulations, Value Added Medicines (VAMs), biosimilars, but are included in the overall statistics. Further analyses in the report in areas of company launch and commercialization performance does not include such companies.

Emerging biopharma companies make up 80% of the current development pipeline and earned 14% of revenue in 2018

Exhibit 2: Company Segments as a Percentage of Pipeline Projects and Global Sales in 2018



Source: IQVIA Pipeline Intelligence, Jan 2019; IQVIA MIDAS, Dec 2018

- Including both early phase and late phase research, EBP companies account for 80% of R&D activity.
- These companies include a range of strategies from pure innovators to companies focused on developing generics, reformulations and biosimilars, all of which still require some regulatory review of their phase I, phase II or phase III trials.
- Companies which have revenues between $500 million and $10 billion dollars represent only 5% of pipeline but 21% of sales, as the combination of the small and mid-sized segments.
- These companies are often focused on specific niches by therapy area, geography, or commercialization approach, but a subset of these companies are in the process of growing rapidly to eventually have sales above $10 billion.
- Large pharma companies have 64% of revenue globally, taking advantage of their larger resources to select and invest in early-phase research that shows the most promise.
- Large pharma companies represent the largest segment of partners and/or purchasers of companies and products originated by EBP companies.
- The pipeline activity by large companies includes those assets originated in their own labs as well as those already acquired from academia or other smaller companies.

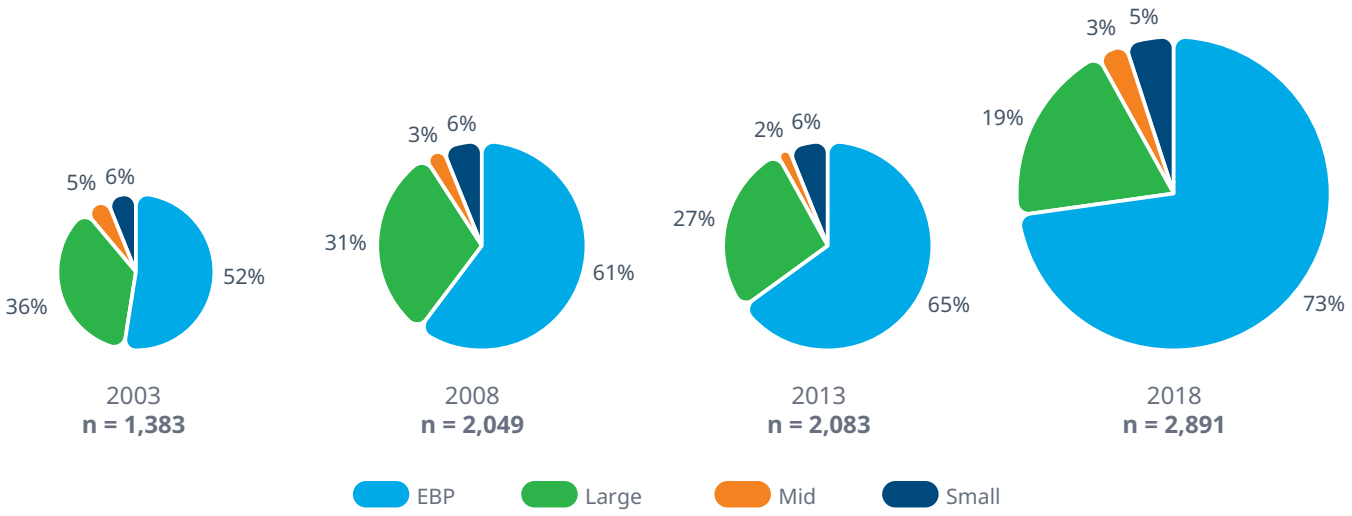
Chart notes: Pipeline products being developed by multiple companies are attributed to the company in the larger revenue segment. Company segment share of sales or pipeline are represented in terms of the share of the area of the triangle. EBPs in this chart include some smaller generic companies, distributors, parallel traders. Some of these companies have no novel compound research but are instead focused on novel formulations, Value Added Medicines (VAMs), biosimilars, but are included in the overall statistics. Further analyses of company performance around launch and commercialization rarely include such companies.

Research and development activities

- Emerging biopharma companies now represent 73% of late-stage research, up from 52% in 2003.
- Emerging biopharma companies also represent 84% of early-phase research and a sharply rising share of late-phase research.
- The late-stage development pipeline of emerging biopharma has steadily expanded with 15% growth in the number of products in both 2017 and 2018.
- With 8,706 products in active development, ranging from discovery to registration, emerging biopharma are developing treatments that span a diverse range of drug classes.
- Oncology late-phase pipelines have increased 74% in the past five years driven by targeted agents.
- Emerging biopharma companies are developing more than 90% of Next-Generation Biotherapeutics in the late-stage pipeline.
- EBP companies also ran 65% of all clinical trials in 2018 and are now running more trials than larger companies across all phases.
- The composite success rate for products developed by emerging biopharma companies is 17% – greater than other company segments.
- The top 30 emerging biopharma companies employ both traditional and cutting-edge technologies that span across therapy areas.
- These EBPs tend to have three major organizational archetypes that may correlate with their approaches to development and commercialization strategies. These include “US-Based Standalone Companies”, largely developing assets to license to other companies; “Hub and Spoke” companies with centralized corporate functions and separate subsidiaries to optimize operations and develop assets across a wide range of therapy areas; and “Ex-US Companies” that are typically regionally focused companies working on biobetter and/or biosimilars or that in-license assets for marketing in emerging markets.
- The top 30 emerging biopharma companies by pipeline employ both traditional and cutting-edge technologies that span across therapy areas.

Emerging biopharma companies now represent 73% of late-stage research, up from 52% in 2003

Exhibit 3: Percentage of Late-Stage Pipeline by Company Segment, 2003–2018



Source: IQVIA Pipeline Intelligence, Jan 2019

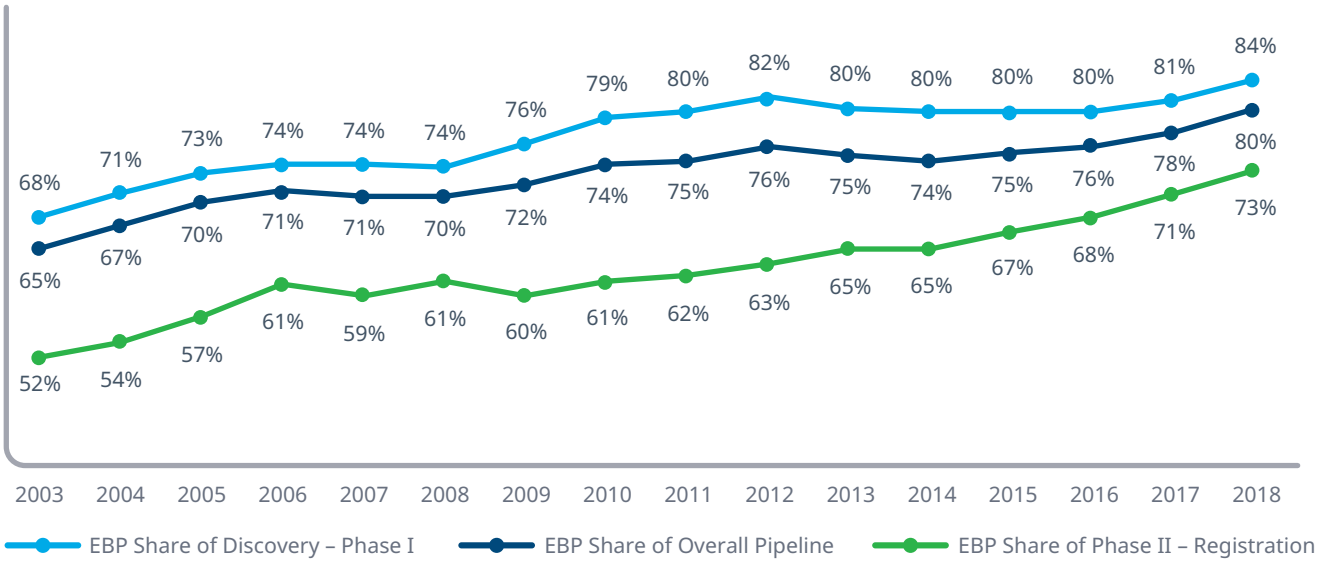
- Emerging biopharma companies accounted for 73% of the total late-stage R&D pipeline in 2018, compared with 61% in 2008.
- Large pharma companies have seen their share drop from 27% to 19% from 2017 to 2018.
- The share of mid-sized and small pharma companies developing novel products has remained steady since 2003, with small pharma developing approximately 5–6% of products and mid-sized pharma developing from 2–5%.
- Emerging biopharma companies are increasing their pipeline share, because they are the most active in the fastest-growing areas of oncology and orphan drugs, and because they increasingly can develop their innovations without the need to partner or be acquired.
- In the past, the majority of EBP assets were sold or licensed before launch. However, in 2018, EBPs themselves launched 47% novel therapies.[1]
- 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: Late-stage pipeline is defined as active programs (activity in past three years) in Phase II through registration. Research programs are considered active following an update for three years unless specific information indicates that research has stopped. Drugs are noted in relation to the most-advanced research phase across indications and geographies. If multiple companies were involved in a project, the larger segment takes precedence. Percentages may not sum to 100% due to rounding.

[1] IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: https://www.iqvia.com/institute/reports/the-changing-landscape-of-research-and-development

Emerging biopharma companies represent 84% of early-phase research but a sharply rising share of late-phase research

Exhibit 4: Emerging Biopharma Share of Early, Late and Overall R&D Pipeline 2003–2018



Source: IQVIA Pipeline Intelligence, Jan 2019

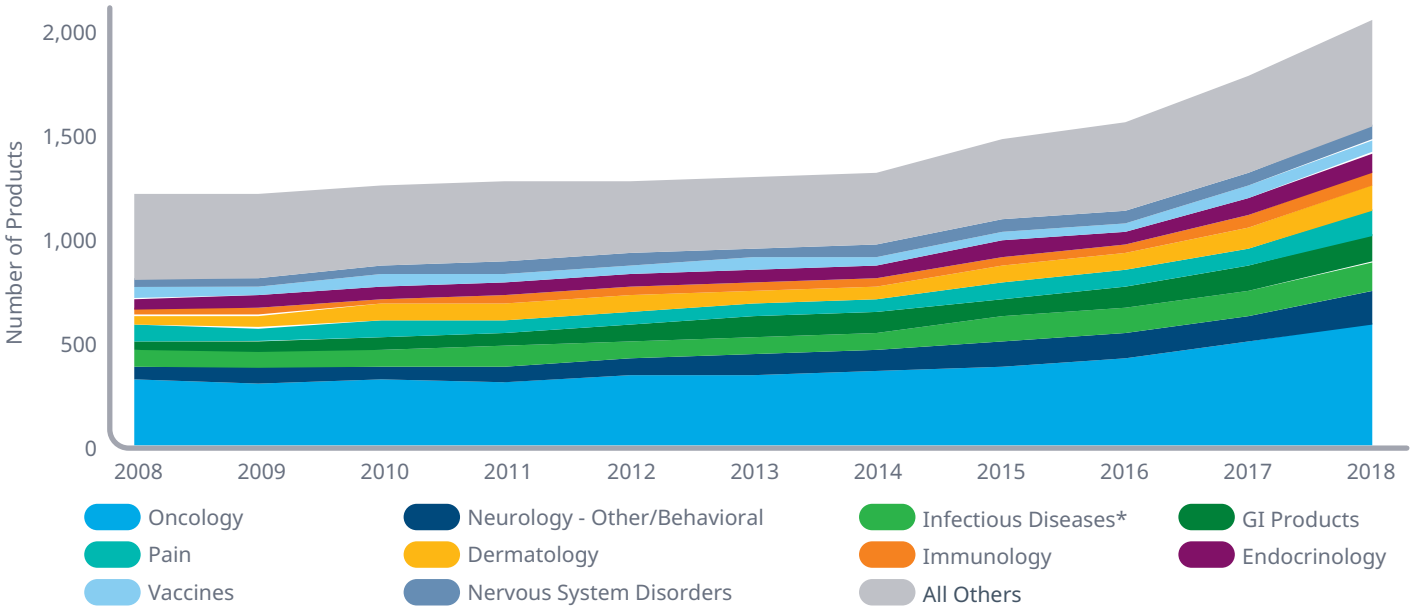
- Over the last 15 years, emerging biopharma companies have seen steady growth in their share of the overall R&D product pipeline. They reached an 80% share of the total pipeline in 2018, up from 65% in 2003.
- Emerging biopharma companies have a growing impact on early-stage development - from discovery through Phase I – with their share of pipeline products increasing from 68% in 2003 to 84% in 2018.
- Late-stage development, from Phase II to registration, has also seen an increase in share, growing from 52% in 2003 to 73% in 2018. This increase mirrors an increase in the number of emerging biopharma companies launching novel products, growing from 33% in 2010 to 47% in 2018.[1]

Chart notes: Research programs are considered active following an update for three years unless specific information indicates that research has stopped. Drugs are noted in relation to the most-advanced research phase across indications and geographies. If multiple companies are involved in a drug program, the company from the larger segment has been shown. The EBP segment shown here do not have partners from Large, Mid or Small-sized pharma companies involved in their programs, but that does not mean there are not commercialization agreements in place that could ultimately result in a comarketing or copromotion.

[1] IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: https://www.iqvia.com/institute/reports/the-changing-landscape-of-research-and-development

The late-stage development pipeline of emerging biopharma has steadily expanded with 15% growth in both 2017 and 2018

Exhibit 5: Number of Late-Stage Emerging Biopharma Pipeline Products by Therapeutic Drug Class, 2008–2018



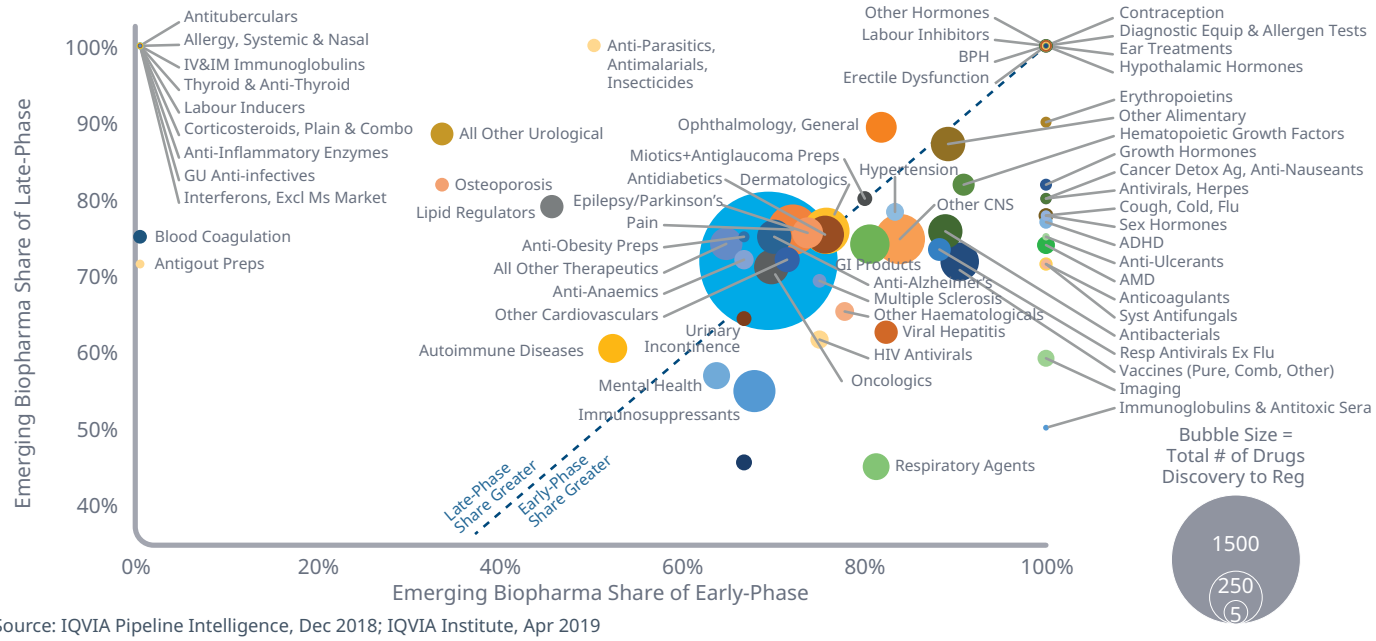
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Mar 2019

- The number of molecules in development by emerging biopharma companies in Phase II or later increased by 15.3% in 2018 to a total of 2,120 molecules, and by 57.5% from 2013–2018, at a CAGR of approximately 9.5% over the same period.
- Almost 30% of late-stage emerging biopharma pipeline products were oncology therapies in 2018. Oncology products developed by emerging pharma companies have grown by 20% since 2017 and 74% since 2013.
- The category "Neurology - other/behavioral," which are therapies for indications such as spinal muscular atrophy, cognitive disorders**, insomnia and epilepsy, made up 8% of the pipeline in 2018 and have grown 69% since 2013, with 31 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 43% since 2013.
- Pain products have increased the most out of all therapy classes since 2017, an increase of 40% through 2018. Pain products made up 6% of the pipeline in 2018 and have increased 76% from 2013. Notably, development in pain has been shifting towards non-narcotic medicines, as pressures to limit and avoid opioid use have strengthened in response to the opioid crisis.

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; GI = Gastrointestinal; **Cognitive disorders under "Neurology – Other/Behavioral" drug class do not contain anti-Alzheimer's therapies.

Emerging biopharma are developing treatments that span a diverse range of drug classes

Exhibit 6: Number of Products and Emerging Biopharma Share of Early and Late-Stage R&D Pipeline, 2018



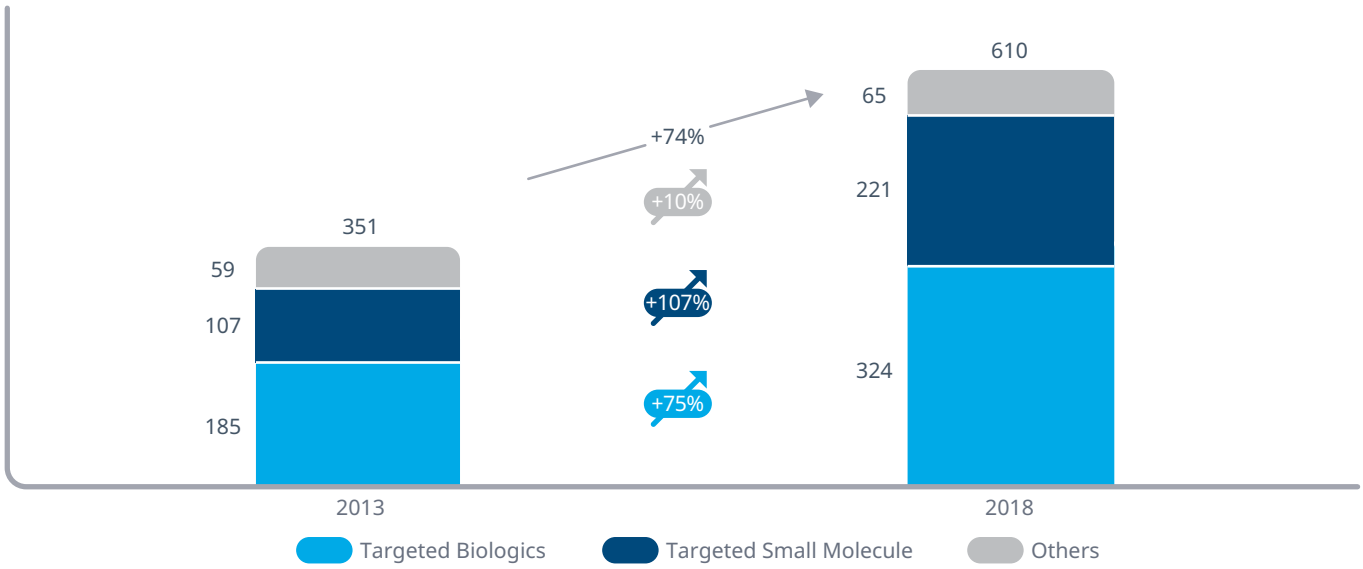
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Apr 2019

- There are currently 8,706 products in active development, ranging from discovery to registration. Emerging biopharma companies currently hold assets across the development spectrum, with greater concentration in certain therapeutic areas with varying degrees of demand.
- Emerging biopharma companies comprise a large portion of both early-stage and late-stage oncology development, at 69% and 72%, respectively.
- The next largest areas of pipeline development include pain, other CNS therapeutics, dermatologics, immunosuppressants and gastrointestinal (GI) products. EBP shares for the early and late-stage pipeline in these areas are on average 70%.
- Small yet critical areas of development, such as hypothalamic hormones and erythropoietins, are dominated by emerging biopharma companies across the pipeline, with shares between 90–100% in both early and late-stage development.
- Emerging biopharma companies have a majority of the late-phase yet little to none of the early-phase pipeline for antituberculars, allergy, thyroid and genitourinary anti-infective assets. These are small areas of development, consisting of only 12 products.
- Similarly, emerging biopharma companies hold a majority share of 17 blood coagulation products in late-phase development, though little to no share of those in early-stage development.

Chart notes: 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. Bubble size represents total pipeline, not just EBP products.

Oncology late-phase pipelines have increased 74% in the past five years driven by targeted agents

Exhibit 7: Number of EBP-Developed Oncology Products in the Late-Stage R&D Pipeline by Drug Type



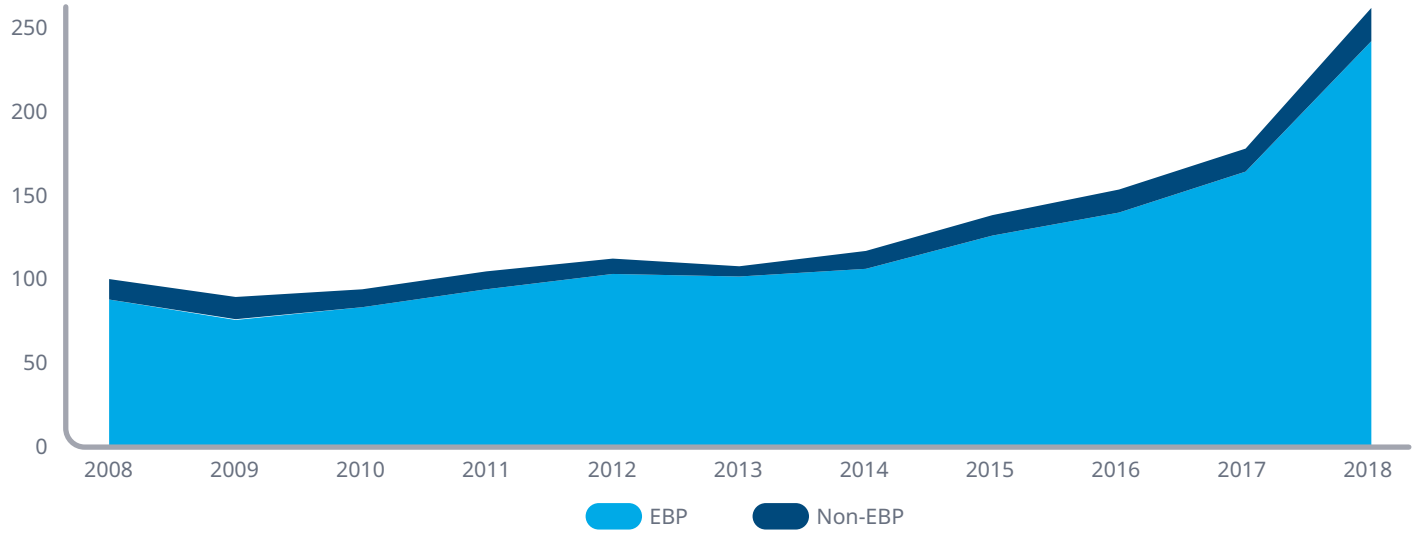
Source: IQVIA Pipeline Intelligence, Dec 2018; IQVIA Institute, Apr 2019

- The number of late-stage pipeline oncology therapies developed by emerging biopharma companies grew from 351 in 2013 to 610 in 2018, an expansion of 74%, due in large part to the growing number of targeted therapies in the pipeline.
- In 2018, 89% of late-stage oncology products being developed by emerging biopharma companies were targeted therapeutics, up from 83% of the pipeline in 2013.
- Targeted biologic therapies increased 75% from 2013 to 2018, while the number of targeted small molecules more than doubled. Other therapies, including radiotherapies and hormonal, have increased more modestly by 10% over the past five years.
- Targeted therapies, including immuno-oncology therapies and small-molecule kinase inhibitors, represent a paradigm shift in the treatment of cancer. Robust growth in this area of oncology products suggests that the range of mechanisms and novel technologies being explored by emerging biopharma companies is increasing.

Chart notes: Therapeutic Oncology pipeline where emerging biopharma companies are the only companies involved in development. Late phase pipeline includes trials in Phase II or higher for the most advanced indication. Phase I/II trials are included as Phase II. Others includes radiotherapies, hormonal therapies and cytotoxic therapies.

Emerging biopharma companies are developing more than 90% of Next-Generation Biotherapeutics in the late-stage pipeline

Exhibit 8: Number of Next-Generation Biotherapeutic Pipeline Products in Late-Stage Pipeline by Company Segment, 2008–2018



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

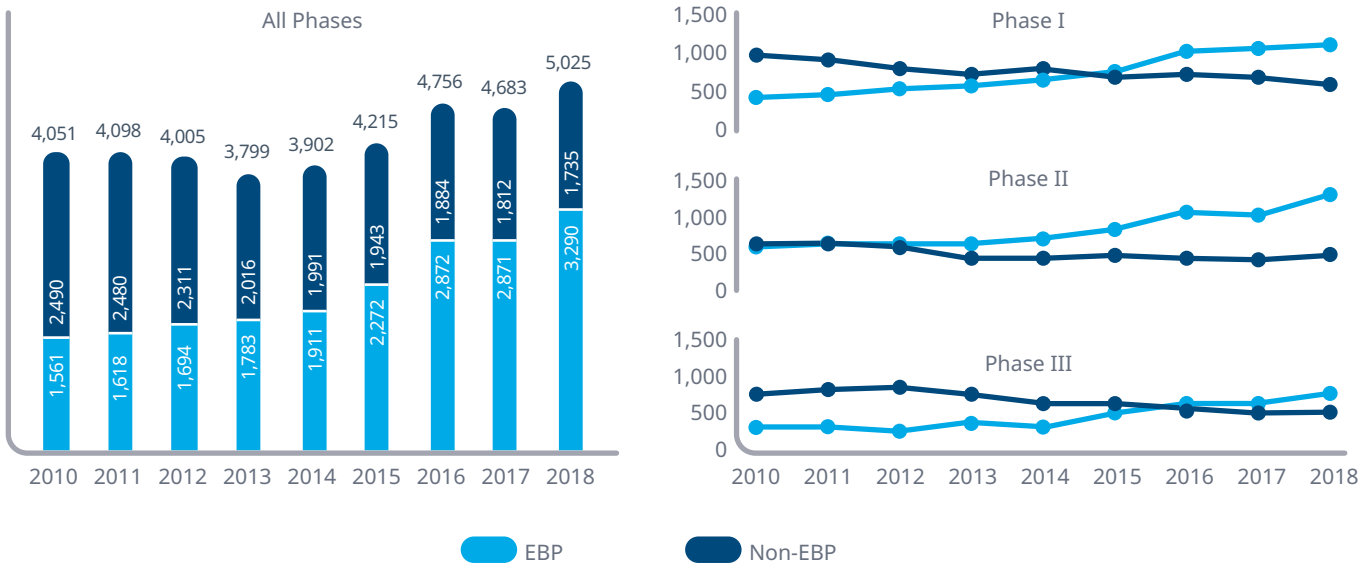
- Next-Generation Biotherapeutics (NGB) – defined as cell, gene and nucleotide therapies – make up less than 10% of the total late-stage R&D pipeline, but have more than doubled in number over the past three years, as new pathways for disease treatment and potential cures command growing attention and investment.[1]
- The total number of NGBs in the late-stage pipeline reached 269 by the end of 2018, up from 182 in 2017, as a number of products moved from Phase I to Phase II.
- Emerging biopharma companies accounted for 92% of the late-stage NGB pipeline, as the startups who have pioneered the dozens of cell and gene therapy approaches have continued to innovate and retain control of their technologies.
- Rather than a distinct drug as the output of research, some of these technologies will produce a patient treatment personalization methodology that must then be scaled up for the market. It is likely that large proportions of these therapeutics will ultimately be licensed to larger companies for commercialization.

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.

[1] IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: https://www.iqvia.com/institute/reports/the-changing-landscape-of-research-and-development

Emerging biopharma ran 65% of clinical trials in 2018 and are now running more trials than larger companies across all phases

Exhibit 9: Number of Clinical Trials by Phase and Company Segment



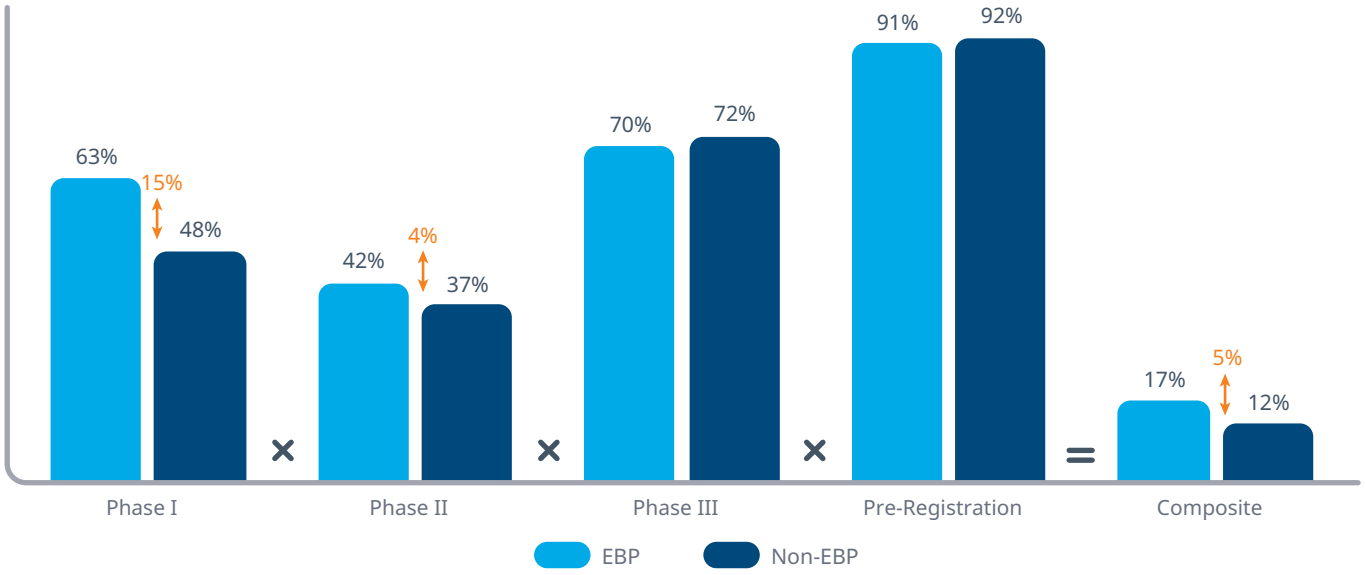
Source: Clarivate Analytics Cortellis, May 2019; IQVIA Institute, May 2019

- From 2010 to 2018, the number of clinical trials run by emerging biopharma companies has more than doubled to 3,290 trials, representing 65% of trials started in 2018.
- The greatest increases in the number of emerging biopharma trials has been in Phase I and Phase II, with 2.5 times more trials and 2.1 times, respectively.
- The number of Phase III trials being run by emerging biopharma has increased more slowly, but has still grown 75% since 2010.
- The percentage of emerging biopharma run clinical trials has increased across all therapy areas. In particular, the share of emerging biopharma trials out of all trials has increased significantly in endocrinology, psychiatry, respiratory, rheumatology and transplantation, with growth rates of over 100% from 2010 to 2018.
- The EBP share of oncology trials has increased from 43% in 2010 to 65% in 2018, demonstrating that emerging biopharma companies are becoming more capable of running these more complex studies.

Chart notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials were excluded from the analysis. Totals for 2018 may be reflecting delayed filing of those trials into trial databases. Non-EBP includes companies with R&D spend > $1.5Bn or Rx Sales >$5Bn and companies with R&D spend between $200Mn - $1.5Bn OR Rx sales between $400Mn - $5Bn. Emerging biopharma (EBP) companies have R&D spend < $200Mn or Rx sales between $50Mn - $400Mn or number of trials since 2014 > 0. EBP companies in the older years may understate EBP, as the segmentation in this analysis was conducted in 2018 and does not account for companies' transactions in prior periods.

The composite success rate for products developed by emerging biopharma companies is 17% – greater than other company segments

Exhibit 10: Average R&D Composite Success Rate and Average Success Rates per Phase, 2014–2018



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

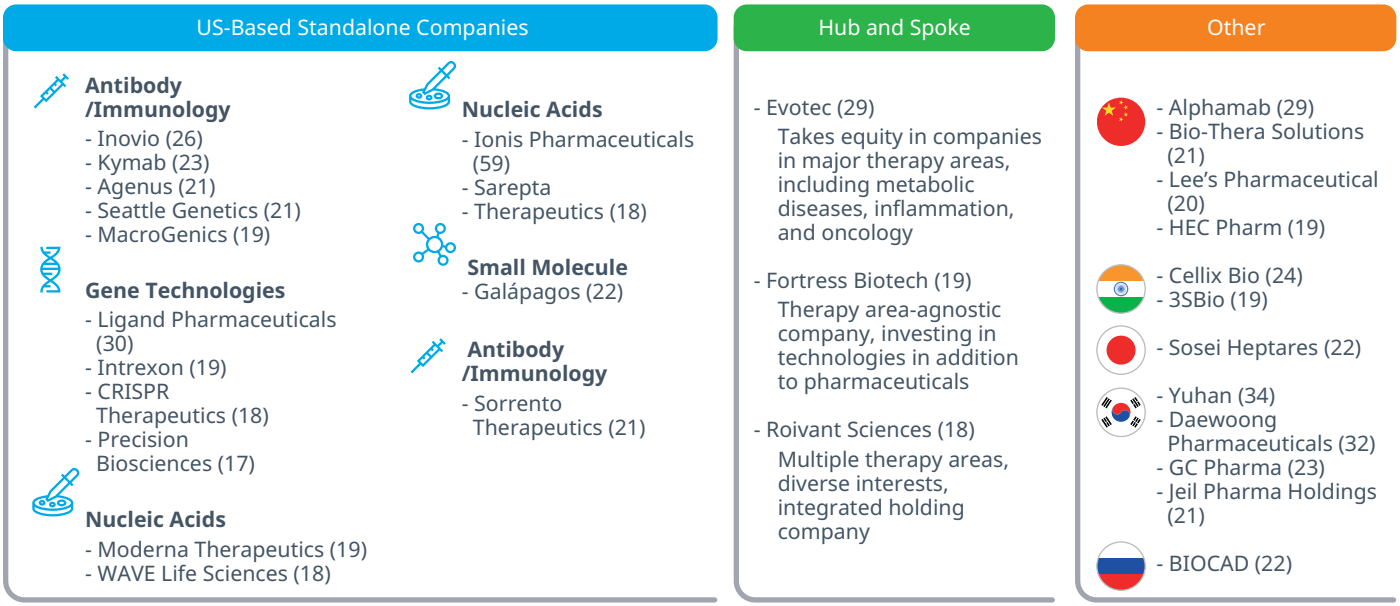
- The composite success rate of clinical development from Phase I trials to regulatory submission – based on the percent of drugs successfully progressing to each next stage of development – was 11.4% in 2018 for all company segments, down from 14.4% in 2017.[1]
- Emerging biopharma companies achieved a composite success rate of 17.2%, higher than the 12.1% of other company types, reflecting their greater success across Phase I development relative to other company segments.
- There was a 15.5% difference in success rates between emerging biopharma companies and other company segments in Phase I, and a 4.3% difference in Phase II, reflecting the critical role emerging biopharma companies are playing in early-stage development in R&D.
- Larger pharma companies are more likely to acquire or partner with an emerging biopharma company in later stages, as the potential of the pipeline candidate has been established.
- Phase III and pre-registration rates are slightly lower for emerging biopharma companies. This could indicate that emerging biopharma companies have fewer resources available to move new products through later-stage development.

Chart notes: Numbers may not sum to totals due to rounding.

[1] IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: https://www.iqvia.com/institute/reports/the-changing-landscape-of-research-and-development

The top 30 emerging biopharma companies employ both traditional and cutting-edge technologies that span across therapy areas

Exhibit 11: Top Emerging Biopharma Companies by Focus in Each Organizational Archetype



Source: IQVIA Pipeline Intelligence; IQVIA Institute, May 2019

- There are currently 3,212 emerging biopharma companies collectively investigating 6,965 assets. Of these, 47% are investigating a single asset, while another 40% are investigating 2–10 assets each.
- The top 30 emerging biopharma companies by number of compounds/programs in any stage of R&D account for 703 products, or 8.1% of all products under investigation.
- All of the U.S.-based companies are currently developing medicines and indicate that they will pursue licensing or partnership to commercialize them, though some have pursued marketing of their assets directly. A prime example of this archetype is Ionis, the largest of any emerging biopharma company with 59 assets in development.
- "Hub and Spoke" companies are also U.S.-based but distinctly have centralized corporate functions, but separate subsidiaries for assets. These companies have invested in a wide range of therapy areas, and capitalize on their management and organizational hub model to optimize operations.
- Another twelve companies are ex-US based companies developing biobetters and/or biosimilars, or in-licensing assets for marketing in emerging markets.
- Oncology is the major focus for 21 of the top 30 companies but areas of focus also include therapy areas such as infectious disease, rare diseases and vaccines.
- Companies in the top 30 specializing in gene technologies, including gene therapy, gene editing and epigenetics, are found exclusively in the United States.

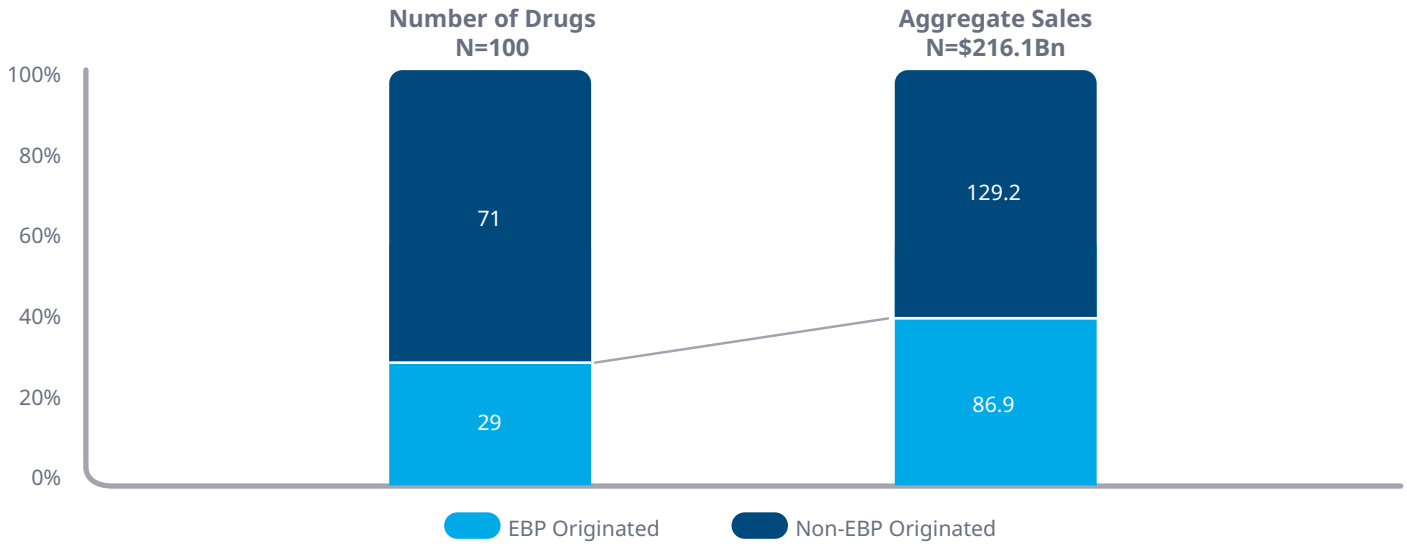
Chart notes: Top 30 companies were determined by number of products in any stage of development, ranging from discovery to registration. Does not take into account assets being investigated for multiple indications in different therapy areas.

Commercialization performance

- Emerging biopharma have patented 29 of the top 100 drugs, which account for 40% of sales in the United States in 2018.
- Emerging biopharma companies originated and launched 42% of new drugs in 2018, a higher percentage than in past years, up from 26% in 2017.
- Of the 59 new active substance (NAS) launches in 2018, 64% were originated by emerging biopharma.
- Over half of EBP-launched drugs had orphan designation and almost a quarter were approved based on a single-arm trial.
- The median time for EBP companies to launch new drugs was 16.6 years in 2018, over 30% slower than other company segments.
- EBP-originated products generally reach the market faster if they were acquired. Particularly assets that were initially owned by an EBP but submitted and subsequently launched by a large pharma company spent less time in development compared to those owned, developed and launched by an EBP.
- For newly launched active substances originated by EBP companies, more address areas of high unmet need; 69% of EBP originated drugs were focused on areas of high unmet need compared to 65% of drugs from other companies.
- Launch performance varies significantly based on unmet need in the market and level of product differentiation
- Emerging biopharmas generally achieve lower average sales when launching new active substances than other companies.
- Average quarterly sales uptake at one year after launch is 2.6 times higher for larger companies launching emerging biopharma-originated products than for emerging biopharma companies who develop and launch their own assets, widening to 6.5 times higher 18 months later.

Emerging biopharma have patented 29 of the top 100 drugs, which account for 40% of sales in the United States in 2018

Exhibit 12: Sales of the Top 100 Drugs in the United States in 2018 by Originator Company Segment

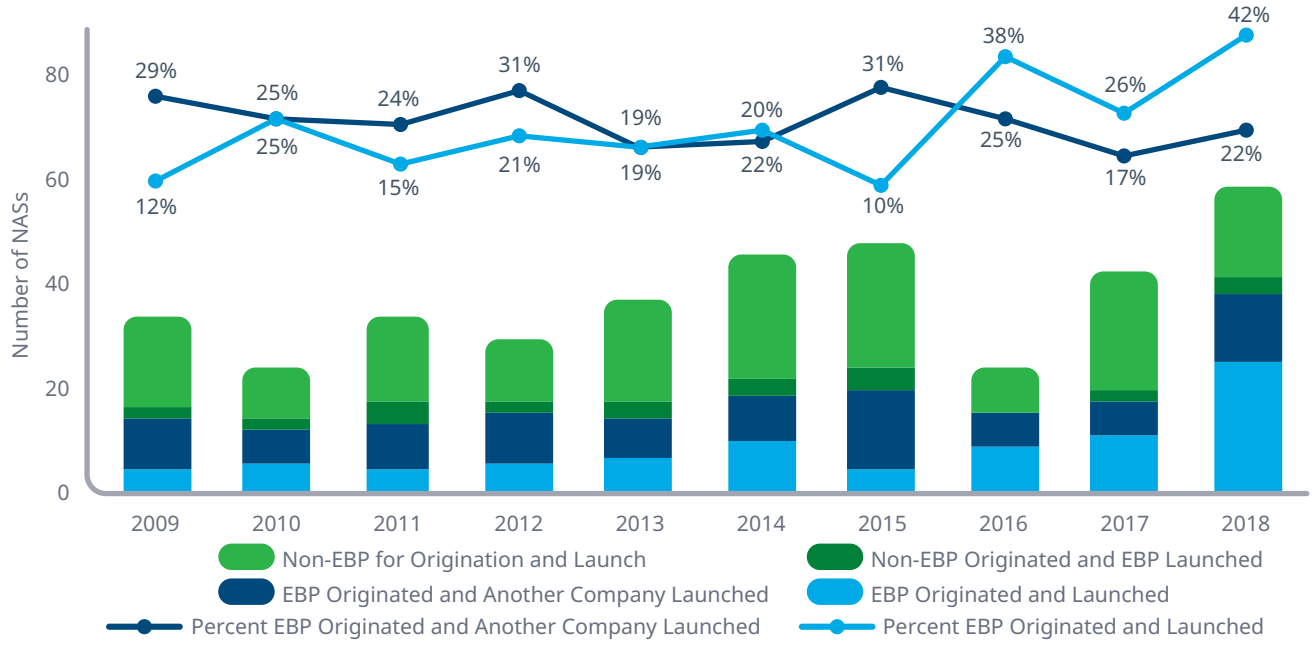


Source: IQVIA MIDAS, Dec 2018; IQVIA Institute, Apr 2019

- Emerging biopharma companies originated 29 of the top 100 drugs in the United States in 2018 but were never the company to launch the drugs.
- These larger selling drugs have universally been launched or marketed by larger companies.
- Emerging biopharma originated drugs have a larger share of sales at 40%, as they generally average higher sales per product than non-emerging biopharma originated drugs.
- Four of the top five drugs in the United States in 2018 were originated by an emerging biopharma company but launched by a larger company.
- Emerging biopharma originated drugs account for 55% of the sales in the top 20 and include such leading drugs as adalimumab (Humira) and etanercept (Enbrel), the top two drugs by sales overall and the top two autoimmune biologics.
- Of launches in the past five years originated by emerging biopharma companies, the highest ranking by sales is the so-called 'quad' pill for HIV, cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide (Stribild), with $4.5 billion in 2018 sales in the United States and ranked 9th overall.
- The immuno-oncology checkpoint inhibitors pembrolizumab (Keytruda) and nivolumab (Opdivo), ranked 11th and 12th in sales in the United States in 2018, and this illustrates an important dynamic related to emerging companies, as the history of both drugs dates back to smaller emerging companies at one point, but arguably the compounds emerged into public view at different stages.
- Nivolumab was developed by the emerging biopharma company Medarex, while pembrolizumab was developed at Organon, which was a larger company by the time the compound emerged and was then purchased in a series of mergers to ultimately be marketed by Merck.

Emerging biopharma companies originated and launched 42% of new drugs, a higher percentage than in past years and up from 26% in 2017

Exhibit 13: Companies Originating and Filing FDA Regulatory Submissions for NASs and Percent of Launches by NAS Launch Year



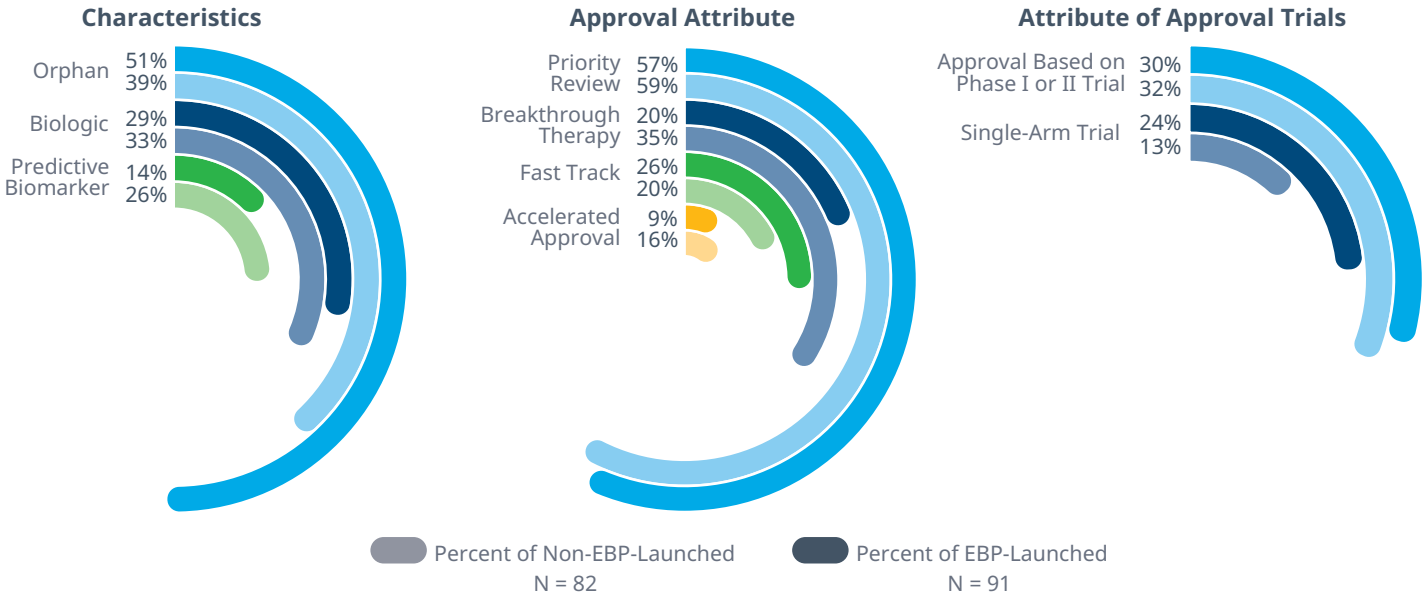
Source: IQVIA Institute, May 2019

- In 2018, 64% of the 59 NAS launches were originated by emerging biopharma.
- EBPs also originated and launched 42% of new drugs in 2018, up from 26% in 2017.
- An increasing number of launches were originated by EBP companies with 50%, 110 of the 219 launches in the past five years compared to 43% of the 158 in the prior five years.
- The 62% increase in the absolute number of EBP-originated launches in the past five years compared to the prior five years reflects a sustained level of investment in these companies over the last few decades.
- Of the products originated by EBPs, they are retaining and launching more of them, launching 55% of originated products in the past five years compared to 41% in the prior five years.
- While larger company launches have varied in number significantly, EBP companies have been steadily launching products, and in increasing numbers, reflecting the significant share of the pipeline they represent and a greater level of strategic interest in marketing their assets themselves.

Chart notes: 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. Chart growth lines exclude percent of EBP launched but originated by other companies.

Over half of EBP-launched drugs had orphan designation and almost a quarter were approved based on a single-arm trial

Exhibit 14: Percent of EBP- and Non-EBP-Launched NASs in the United States 2015–2018 with Each Feature



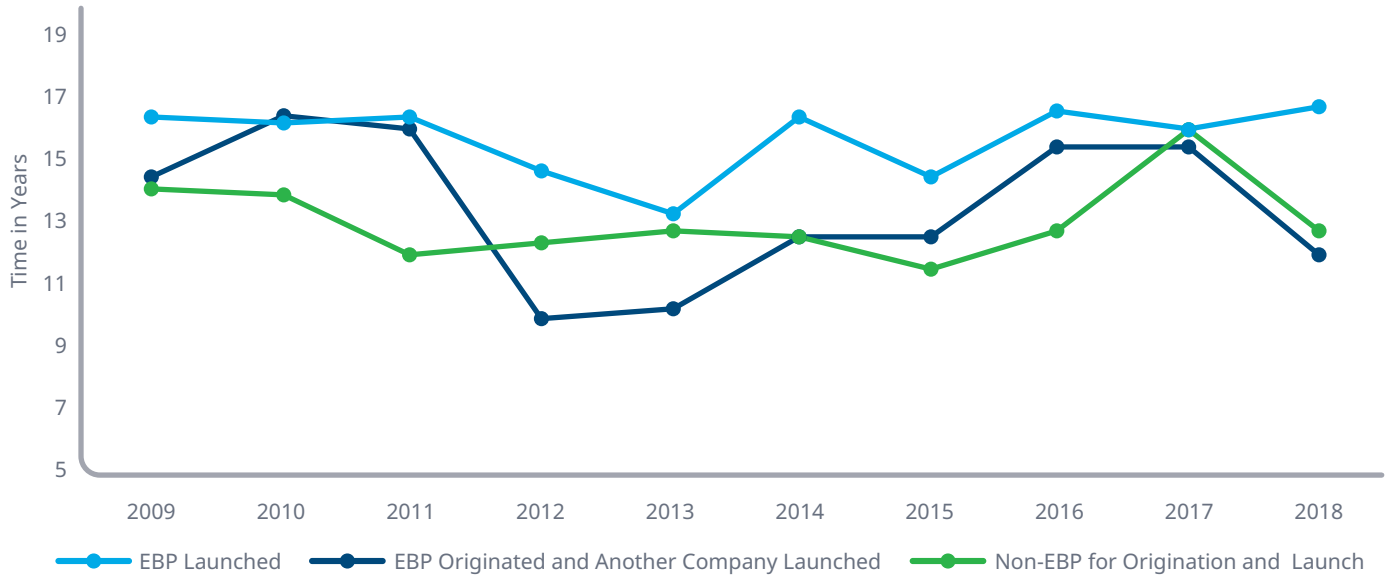
Source: IQVIA Institute, May 2019

- A higher percentage of new drugs launched by emerging biopharma companies from 2015-2018 were orphan drugs, were approved based on single arm trials or had fast-track status, as compared with those launched by non-EBP companies.
- Over half of the 91 NASs launched by EBPs (n=46) in this period were orphan drugs, suggesting the scope of commercial activities and their likelihood of success may be more attainable or appealing to small EBP companies with limited resources.
- Emerging biopharma companies launched twice the number of NASs approved based on single-arm trials (n=22), versus launched by non-EBP companies (n=11), likely driven by the high rates of orphan drugs developed where control arms are less utilized.
- A lower percentage of drugs launched by emerging biopharma companies had predictive biomarkers, were biologics, had accelerated approval or were breakthrough therapies than those launched by non-EBP companies.
- Non-EBP companies launched nearly double the percentage of NASs with predictive biomarkers (26%, n=21) versus EBPs (14%, n=13) suggesting that larger companies may see greater value in precision-medicine assets and acquire them at an early-stage from EBP originators.
- Non-EBP companies launched 61% more breakthrough therapies (n=29) than non EBPs (n=18) from 2015-2018.
- Non-EBP companies launched 13 drugs with accelerated approval compared with the 8 drugs launched by EBPs in this period.

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 2015-2018 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. 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. For regulatory designations (priority, breakthrough, fast track, accelerated approval, approval based on Phase I or II trial, or single arm trials) these are based on announcements by the FDA.

The median time for EBP companies to launch new drugs was 16.6 years in 2018, over 30% slower than other company segments

Exhibit 15: Median Time Per Year from First Patent Filing to Launch by NAS Launch Year, United States



Source: IQVIA Patent Intelligence; IQVIA Institute, May 2019

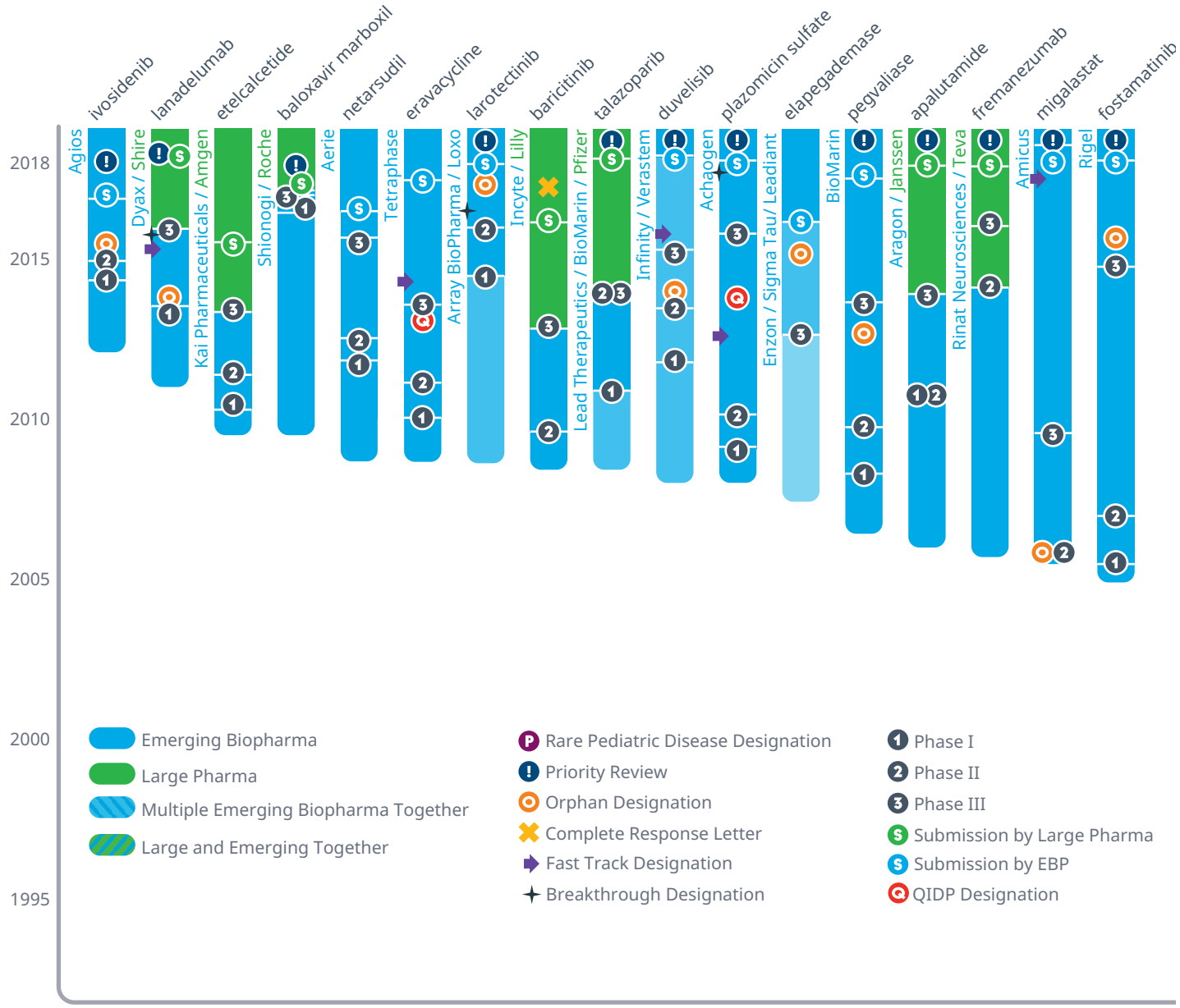
- Development of new drugs remains a slow process. In the United States in 2018, NASs took a median of 13.7 years to launch from the time of their patent filing, when assessed across all company segments.[1] However, the median time from patent to launch for products launched by emerging biopharma companies is 16.6 years.
- From 2013 through 2018, median patent to launch timelines have increased 26% for products that were launched by emerging biopharma companies, however, when viewed since 2009, median patent to launch for products within this segmentation has been relative stable.
- In 2018, products originated by an emerging biopharma company but launched by a different company had a median time from first patent to launch of 12.6 years. This value is similar to products not originated or launched by emerging biopharma companies, at 11.9 years.
- Overall, these patent to launch times suggest that emerging biopharma companies face challenges when launching products, while other companies have access to resources that allow them to reach the market sooner.

Chart notes: Compares the date of patent filing for a medicine to FDA approval for a specific indication. EBP launched includes products that were originated by an emerging biopharma company or another company segment.

[1] IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: https://www.iqvia.com/institute/reports/the-changing-landscape-of-research-and-development

Emerging biopharma originated products progressed to launch with a variety of pathways, development events and durations

Exhibit 16: New Active Substances Launched in the U.S. and Originated by Emerging Biopharma



Source: IQVIA Patent Intelligence; IQVIA Pipeline Intelligence; IQVIA Institute, May 2019

Emerging biopharma originated products progressed to launch with a variety of pathways, development events and durations continued

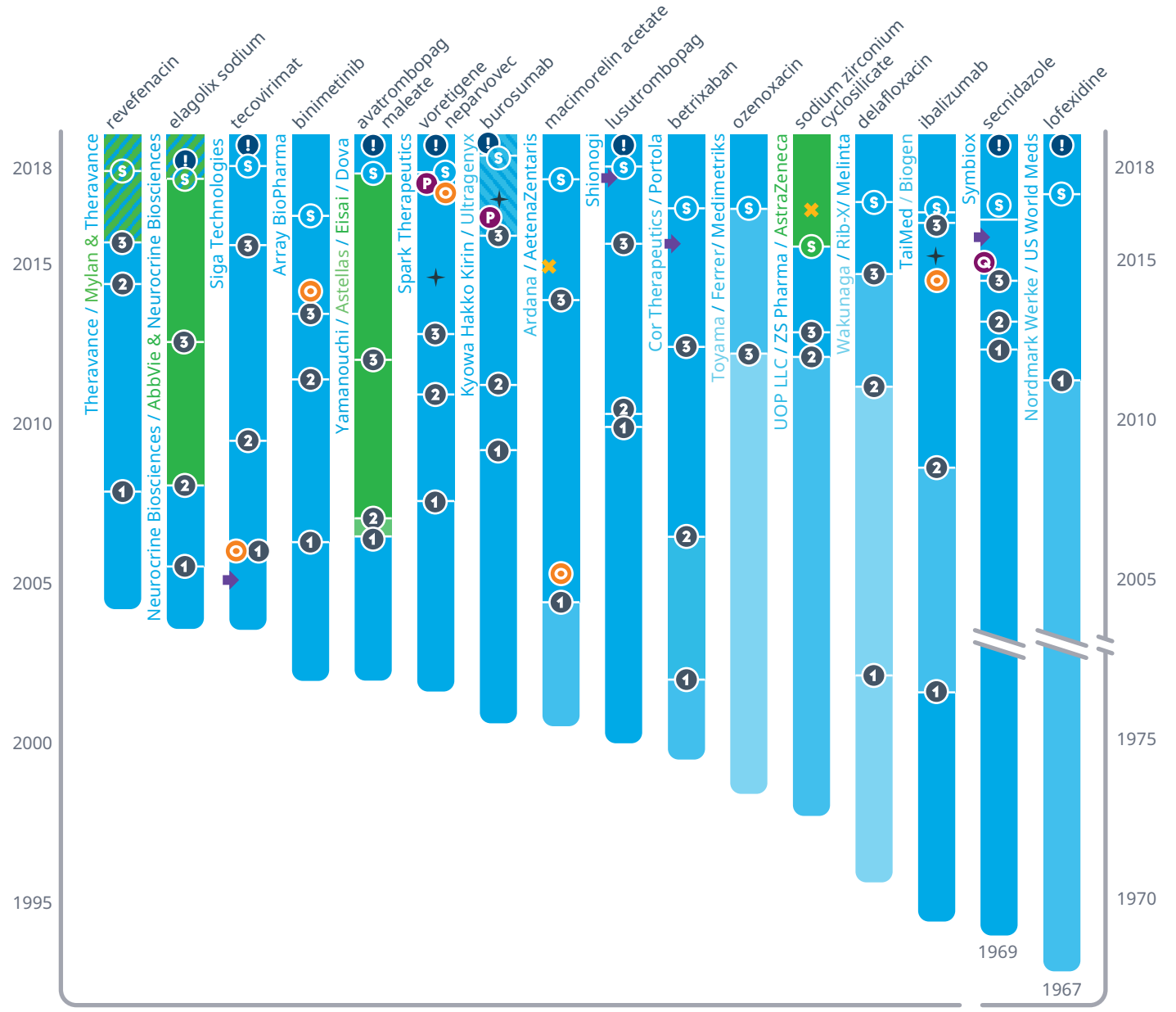


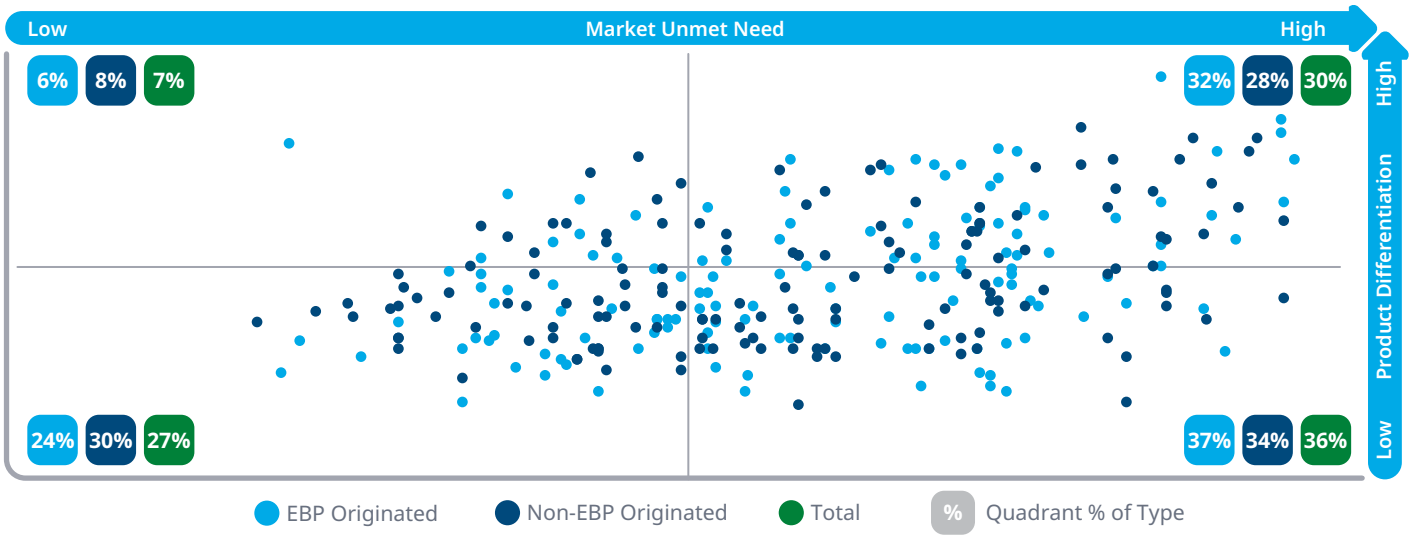
Chart notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new. There were no mid-sized or small companies involved in the assets tracked on the prior two pages. Designations flagged on the prior pages are FDA designations including rare pediatric, fast track, breakthrough, orphan, and qualified infectious disease (QIDP). Priority review are noted when they were announced. Phase I, II, III start have been included where identified as the first phase start across indications and geographies. Submission is based on the date companies announced filing with the FDA. Complete response letters are provided by FDA as a conclusion to an application, but allow the applicant to resolve the issues and resubmit, which occurred in all three instances analyzed. Companies who jointly filed with FDA have been indicated with combined coloring in the timeline.

Emerging biopharma originated products progressed to launch with a variety of pathways, development events and durations continued

- A subset of 33 NAS products across therapy areas are shown, demonstrating differences between the development and regulatory journey of assets developed and launched by EBPs versus those licensed/sold to a large company. Ten of these products originated with an EBP, but were launched by a large company, while the remaining 23 products were developed and launched by an EBP.
- Assets initially owned by an EBP but submitted and subsequently launched by a large pharma company generally spent less time in development compared to those owned, developed and launched by an EBP. Large pharma companies entered into partnerships and/or acquisitions with EBPs in late-stage development, when risks associated with early-stage development were resolved.
- Phases I and II appear to be the biggest determinants of time to launch, as Phase III timeline is relatively consistent.
- Partnerships between EBPs or an EBP and large pharma only occurred in Phase III or at submission in this subset, when developmental and regulatory timelines are less variable.
- The development time of products with more than two companies involved appears to lengthen, as seen with ozenoxacin, sodium zirconium cyclosilicate and delafloxacin.
- Patent shelf delays developmental time, however, once development begins, there is little to no effect on time from Phase I to launch.
- Certain attributes, such as orphan designation or breakthrough designation, are not awarded until the end of the development cycle, and therefore have little impact on the overall development timeline. Similarly, fast track designation is awarded relatively late in the developmental timeline and does not have a strong impact on the overall timeline, though it may increase the probability of approval.
- While priority review lessens the time from submission to launch, there is little effect on the overall development time, as products with both short and long developmental timelines received priority review.
- Additionally, the receipt of a complete response letter, while lengthening the time from initial submission to launch, does not necessarily significantly impact the development timeline.
- Products with high unmet need, such as netarsudil for glaucoma, and eravacycline for certain antibiotic-resistant infections, demonstrated a relatively quick and uncomplicated developmental journey, despite a lack of designations designed to lessen time to approval and launch.
- Novel products, such as the gene therapy voretigene neparvovec, do not necessarily experience significant development time increases or decreases, as development of this product is consistent with the median time from first patent to launch.
- The variation in time between submission and launch reflects both the length of time for regulatory review and, in some cases, delays while reimbursement issues for the product are resolved prior to the launch.

For newly launched active substances originated by EBP companies, more address areas of high unmet need

Exhibit 17: U.S. New Active Substance Launches by Originating Company Type, 2008–2017



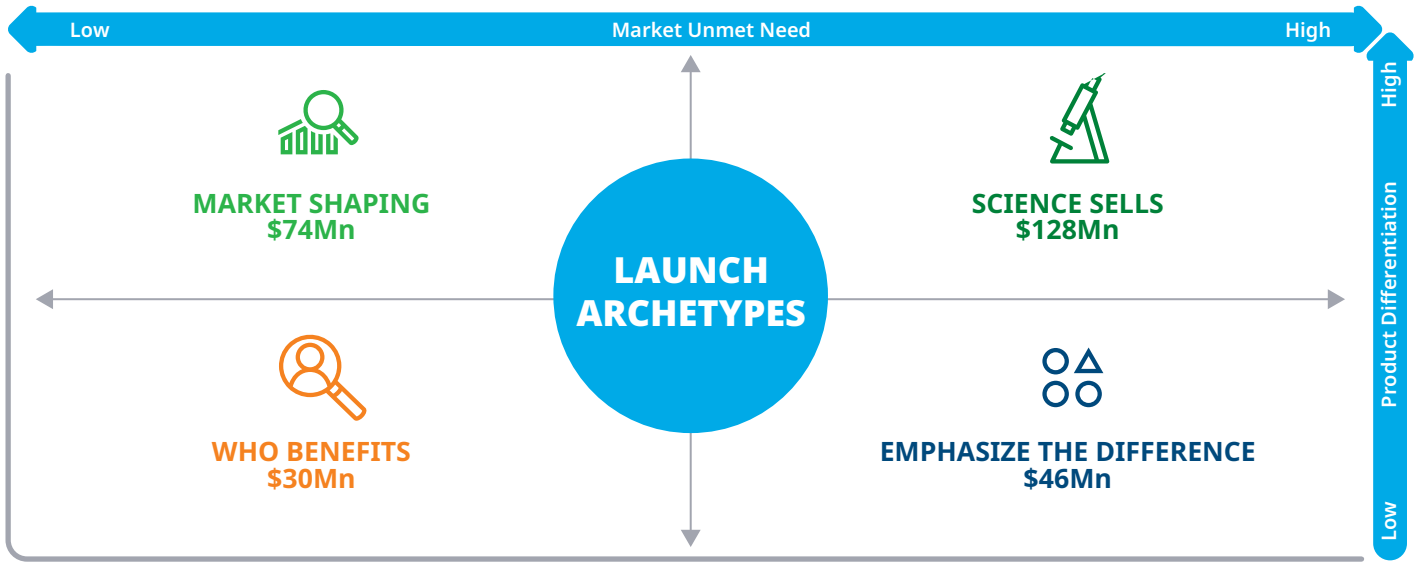
Source: IQVIA. Creating a framework for a successful launch: Planning and preparing. Jul 2018
Available from: https://www.iqvia.com/blogs/2018/07/creating-a-framework-for-a-successful-launch

- Of the 291 NAS assessed launches between 2008 and 2017, 139 were originated by an emerging biopharma company, and 152 by other companies.
- EBPs originate more differentiated, high unmet need medicines, 32% of all of their launches and 45 products overall compared to 43 medicines or 28% of non-EBP originated drugs.
- Overall, 69% of EBP originated drugs were focused on areas of high unmet need compared to 65% of drugs from other companies.
- Of the most differentiated and unmet need drugs originated by EBPs, 60% (27) of them were licensed or sold to and launched by other companies.
- EBPs retained 45 of the 85 drugs they developed, which were of lower product differentiation, perhaps reflecting less market interest in these assets.
- Non-NAS products are generally reformulations or combinations of existing medicines, and EBP companies have demonstrated an ability to identify and demonstrate the value of these products. EBP companies filed the specific patents on 53% of the 262 non-NAS products launched between 2008 and 2017 (not shown).
- Sixty percent of non-NAS launches were in areas with lower unmet need and with relatively low product differentiation, and EBPs launched 92 of these 165 drugs, suggesting an important sub-segment of EBP companies are pursuing niche markets with more complicated marketing messages.
- Of the 15 non-NASs, which were both highly differentiated and filled a high unmet need, EBPs originated 12 of them and launched seven of them, licensing or selling the other five, and other companies developed and launched the other three.
- Of the 64 drugs with high unmet need but lower product differentiation, EBPs originated 41 of them and launched 26, as well as launching a further seven originated by other companies.

Chart notes: A New Active Substance (NAS) is a new molecular or biologic entity or combination where at least one element is new.

Launch performance varies significantly based on unmet need in the market and level of product differentiation

Exhibit 18: EBP Launch Archetypes and Average First-Year Sales 2008–2017



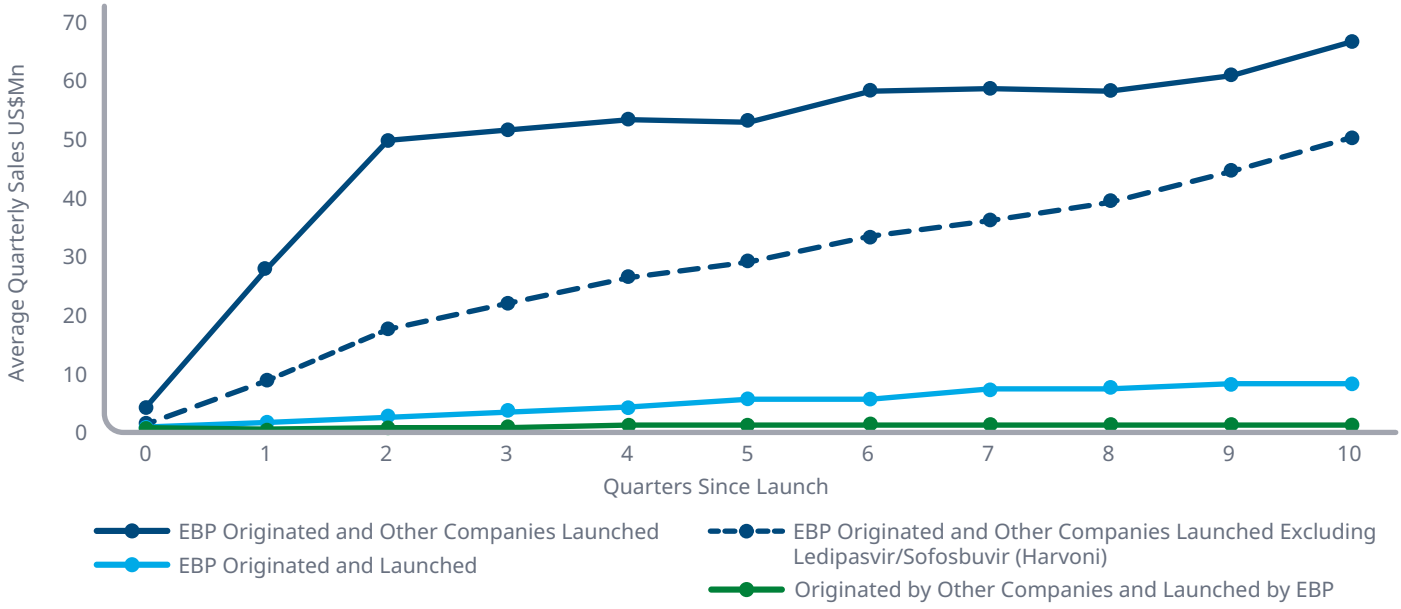
Source: IQVIA. Creating a framework for a successful launch: Planning and preparing. Jul 2018.
Available from: https://www.iqvia.com/blogs/2018/07/creating-a-framework-for-a-successful-launch

- In analyzing launches, the characteristics of the therapy area and the product highlight some distinct differences in the market environment and potential of the products. The names of the resulting quadrants suggests common market approaches to drugs fitting those attributes.
- "Unmet Need" in a therapy area includes the efficacy of the standard of care, as well as some of the existing challenges in treating patients, such as side effects, dosing, overall quality of life and the disease's burden to the health system.
- "Product Differentiation" was assessed based on each launched product's clinical improvement over the standard of care at the time of launch, as demonstrated in clinical trials. Tolerability, dosing advantages and the novelty of the mechanism of action relative to the current standard of care were all assessed to determine a product differentiation result.
- For non-emerging biopharma launches, the average first-year sales for the "Science Sells" group is $174 million, 36% higher than emerging biopharma companies, which average $128 million. In the 'Market Shaping' group, first-year sales are $105 million, 42% higher than EBPs at $74 million.
- The "Emphasize the Difference" products, when launched by larger companies averaged 63% higher first year sales at $75 million compared to $46 million by EBPs.
- "Who Benefits" products, which are undifferentiated with low overall unmet need, launched by EBP companies averaged $30 million in first-year sales, less than half of the $74 million averaged by larger companies.

Chart notes: Viral hepatitis excluded from averages.

Emerging biopharmas generally achieve lower average sales when launching new active substances than other companies

Exhibit 19: New Active Substances Launched 2014–2018 Originated or Launched by EBP Companies



Source: IQVIA MIDAS, Dec 2018

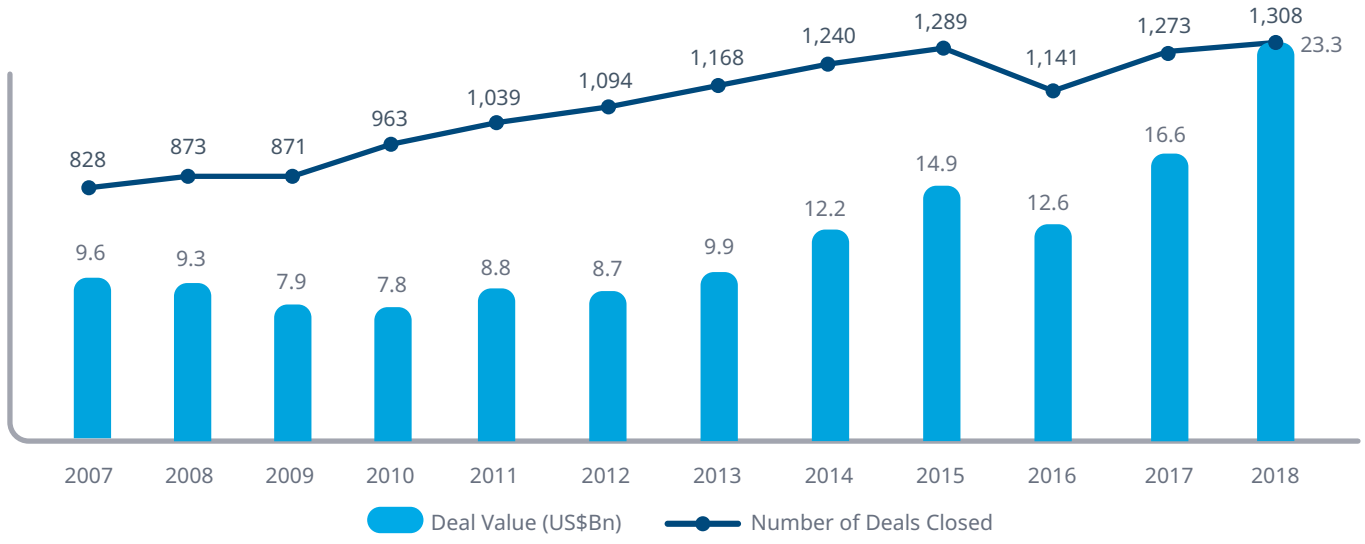
- Some of the most successful new drugs of the past five years were discovered by emerging biopharma companies and later launched by larger companies.
- For launches in the United States since 2013, excluding ledipasvir/sofosbuvir (Harvoni), the average quarterly sales uptake at one year after launch is 2.6 times higher for larger companies launching emerging biopharma-originated products than for emerging biopharma companies who develop and launch their own assets, and 6.5 times higher just 18 months later.
- An increasing number of emerging biopharma launches are orphan drugs, often with low sales, as target populations are often small and hard to diagnose.
- A quarter of the NASs launched by emerging biopharma companies have been in areas of low unmet need and low product differentiation, correlating with lower average sales.
- For emerging biopharma-launched products, only six have a quarterly sales period above $20 million in the five years after launch, with three achieving that within a year of launch.

Strategic transactions

- U.S. venture capital activity in life sciences has been rising in absolute terms and the number of deals.
- In 2018, 1,308 life science venture capital deals were closed with an overall value of over $23 billion, an all-time high resulting from a sharp increase in the past five years, represented by a five-year CAGR of 15%.
- Collaborative R&D deals in 2018 all involved large companies partnering with EBPs.
- The number of collaborative deals has been declining while absolute deal values have risen.
- The number of disclosed collaborative R&D deals fell by 12% from 2017 to 2018, while the aggregate total value of those deals increased to $47.3 billion, with the mean total deal value increasing 8% in 2018 to $569 million.
- EBPs partnering with large companies accounted for nine of the top ten deals in 2018.
- Licensing deals for therapeutics typically occur earlier in a product's development, though 2018 had some notable late-phase deals.
- Discovery stage and Phase I grew 10% and 20%, respectively, from 2017 to 2018, and Phase III licensing activity decreased by 19% from 2017 to 2018, with 50 deals signed in 2018 compared to 62 in 2017.
- There was a 78% increase in deals at pre-registration, up to 62 deals from 36 in 2017.
- Seven of the top ten deals in 2018 involved an emerging biopharma company.
- Deals announced in 2018 included 415 in-licensing or in-bound partnership agreements totaling $272 billion in agreed payments
- On average, companies carried out 9.2 deals each, with deals summing to an average of $6 billion per company, and the median deal amount at $2.6 billion.

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

Exhibit 20: U.S. Venture Capital Deal Value in $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 15%.
- 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 period of performance on public markets, including seven of the ten largest IPOs in Q4 coming from the healthcare sector.[2]
- The increase in number and magnitude of venture capital deals has created a positive funding environment for emerging biopharma companies, allowing them to delay the decision to partner or develop an asset alone.

Chart notes: CAGR = Compound annual growth rate.

[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 Capitol Association. NCVA blog. 2019 Jan 15. Available from: https://nvca.org/blog/8-takeaways-8-graphics-historic-2018-venture-capital/

Collaborative R&D deals in 2018 all involved large companies partnering with EBPs

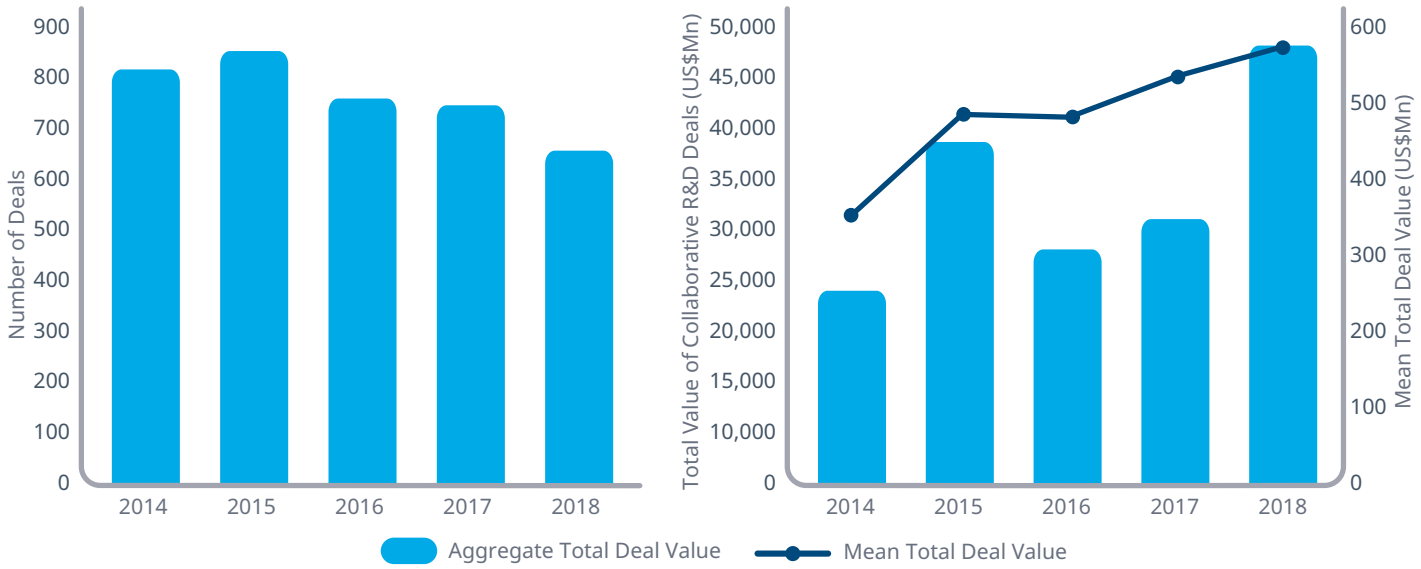
Exhibit 21: Top 10 Therapeutic Collaborative R&D Deals of 2018 by Total Potential Deal Value

TOTAL DEAL VALUE	UPFRONT PAYMENT	COMPANIES	INTEREST AREA	DEVELOPMENT PHASE
$5,096 Mn	$96 Mn in an upfront payment and near-term committed funding	Affimed, Genentech	Natural killer cell engager-based cancer immunotherapeutics using Affimed's ROCK® (Redirected Optimised Cell Killing) platform	Discovery
$3,705 Mn	$200 Mn ($100 Mn cash and $100 Mn equity investment)	Dicerna Pharmaceuticals, Eli Lilly	RNAi therapies for cardio-metabolic disease, neurodegeneration and pain utilising Dicerna's GalXC™ platform	Discovery
$3,150 Mn	$150 Mn	Sangamo Therapeutics, Kite Pharma/Gilead Sciences	Cell therapies for cancer treatment using Sangamo's zinc finger nuclease (ZFN) genome editing technology	Discovery
$1,750 Mn	$50 Mn	Tango Therapeutics, Gilead Sciences	Immuno-oncology therapies derived from Tango's functional genomics-based discovery platform	Discovery
$1,704 Mn	$54 Mn	Immatics Biotechnologies, Genmab	Bispecific cancer immunotherapies discovered using Immatics' Xpresident® technology	Discovery
$1,670 Mn	$60 Mn	Sutro Biopharma, Merck & Co.	Immune-modulating therapies for cancer and autoimmune disorders	Discovery
$1,530 Mn	$110 Mn ($80 Mn cash and $30 Mn equity investment)	Scholar Rock, Gilead Sciences	Inhibitors of transforming growth factor beta (TGFβ) activation for the treatment of fibrotic diseases	Discovery
€1,130 Mn ($1,389 Mn)	€15 Mn ($18.4 Mn)	OSE Immuno-therapeutics, Boehringer Ingelheim	OSE-172 for the treatment of advanced solid tumors	Preclinical
$1,375 Mn	$125 Mn in an upfront payment and near-term milestones	SQZ Biotechnologies, Roche	Antigen presenting cell therapies for the treatment of oncology indications	Discovery
$1,320 Mn	$10 Mn	Fate Therapeutics, Ono Pharmaceutical	Off-the-shelf chimeric antigen receptor T-cell (CAR-T) therapies for cancer treatment	Discovery

Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

The number of collaborative deals has been declining, while absolute deal values have risen

Exhibit 22: Number of Collaborative R&D Deals and Aggregate Value and Mean Total Deal Value of Collaborative R&D Deals



Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

- The number of disclosed collaborative R&D deals fell by 12% from 2017 to 2018, and the aggregate total value of those deals, excluding royalties, reached its highest level of the last five years in 2018, peaking at $47.3 billion.
- The mean total deal value (excluding royalties) of those collaborative R&D deals with disclosed financial terms increased 8% in 2018 to $569 million, also a five-year high, and included 16 deals with a total value more than $1 billion in 2018, up from 12 deals in 2017 at that value.
- Although there were fewer collaborative R&D deals signed in 2018, on average they were of higher total value, and moreover, the median total deal value for such deals has increased 157% over the past five years to $320 million in 2018 – only slightly lower than the high of $322 million in 2015.
- More recently, rather than collaborating on research and development, some big pharma firms prefer to fund early-stage research at biotech companies via option-based deals that leave the R&D in the hands of the biotech company until a defined point in development. Like collaborative R&D deals, these agreements are usually high in total value but heavily backloaded.
- One such deal in 2018, potentially worth $759 million, is the collaboration agreement between Ionis Pharmaceuticals and Roche to develop the antisense therapy IONIS-FB-LRx for the treatment of geographic atrophy (i.e., atrophic age-related macular degeneration [AMD]) and other complement-mediated diseases.

Chart notes: Collaborative deals are defined here as discovery or preclinical stage deals that involve two or more parties actively collaborating on R&D. Disclosed value of deals excludes multicomponent deals where it is not possible to split out the financial terms of the research collaboration element. TVD = total deal value

EBP partnering with large companies accounted for 9 of the top 10 deals in 2018

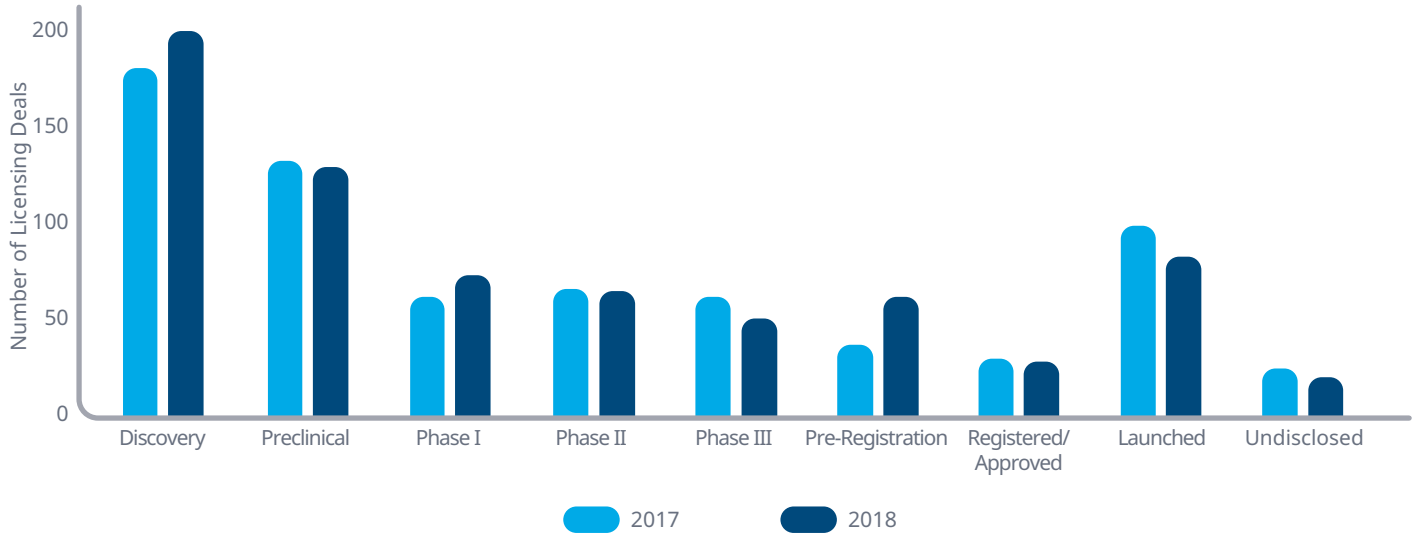
Exhibit 23: Top Partnering Deals (Excluding Settlements and Product Acquisitions) of 2018 by Upfront Consideration

TOTAL DEAL VALUE	UPFRONT PAYMENT	COMPANIES	INTEREST AREA	DEVELOPMENT PHASE
$3,630 Mn	$1,850 Mn ($1,000 Mn cash upfront and $850 Mn equity investment)	Nektar Therapeutics, Bristol-Myers Squibb	Joint development and commercialization of NKTR-214 in combination with Opdivo® (nivolumab) and Opdivo plus Yervoy® (ipilimumab)	Phase II
$1,270 Mn	$1,000 Mn ($375 Mn cash upfront and $625 Mn equity investment)	Ionis Pharmaceuticals, Biogen	Antisense drug candidates for neurological diseases	Discovery
$1,200 Mn	$800 Mn	Arena Pharmaceuticals, United Therapeutics	Ralinepag for the treatment of pulmonary arterial hypertension	Phase III
$5,755 Mn	$750 Mn ($300 Mn cash upfront and $450 Mn reimbursement for R&D expenses)	Eisai, Merck & Co.	Co-development and co-commercialization of Lenvima® (lenvatinib mesylate), both as monotherapy and in combination with Keytruda® (pembrolizumab)	Launched, Clinical stage
$1,800 Mn	$500 Mn ($300 Mn cash upfront and $200 Mn equity investment)	Argenx, Cilag	Cusatuzumab for oncology indications including acute myeloid leukaemia and high-risk myelodysplastic syndrome	Phase II, Phase I/II
$3,750 Mn	$250 Mn ($175 Mn cash upfront and $75 Mn equity investment)	Arrowhead Pharmaceuticals, Janssen Pharmaceuticals	ARO-HBV for the treatment of hepatitis B virus infection; RNAi therapeutics using Arrowhead's TRiM™ (Targeted RNAi Molecule) platform for undisclosed therapy areas	Phase I/II, Discovery
$3,705 Mn	$200 Mn ($100 Mn cash upfront and $100 Mn equity investment)	Dicerna Pharmaceuticals, Eli Lilly	RNAi therapies for cardio-metabolic disease, neurodegeneration and pain utilising Dicerna's GalXC™ platform	Discovery
$2,230 Mn	$170 Mn ($110 Mn cash upfront and $60 Mn equity investment)	Wave Life Sciences, Takeda Pharmaceutical	Nucleic acid therapies for CNS disorders	Phase I/II, Preclinical, Discovery
$2,262.5 Mn	$150 Mn ($100 Mn cash upfront and $50 Mn equity investment)	Prothena, Celgene	Therapies for a broad range of neurodegenerative diseases	Discovery
$1,880 Mn	$150 Mn	Ionis Pharmaceuticals, Akcea Therapeutics	Inotersen and IONIS-TTR-LRx for transthyretin amyloidosis	Pre-registration, Preclinical

Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

Licensing deals for therapeutics typically occur earlier in a product's development, though 2018 had some notable late-phase deals

Exhibit 24: Therapeutic Licensing Deals by Development Stage, 2017 Versus 2018



Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

- An analysis comparing the licensing activity by developmental stage for therapeutic programs in 2017 and 2018 demonstrates reduced licensing in most stages; however, there was an increase in licensing activity for assets in discovery, Phase I, and pre-registration.
- Discovery stage and Phase I grew 10% and 20%, respectively, from 2017 to 2018, while the level of licensing activity for preclinical and Phase II programs remained stable.
- Phase III licensing activity showed a 19% decrease from 2017 to 2018, with 50 deals signed in 2018 compared to 62 in 2017.
- Interestingly, there was a 78% increase in deals at pre-registration, up to 62 deals from 36 in 2017. A majority of these were settlement deals on patent litigation for generic equivalents.

Seven of the top 10 deals in 2018 involved an emerging biopharma company

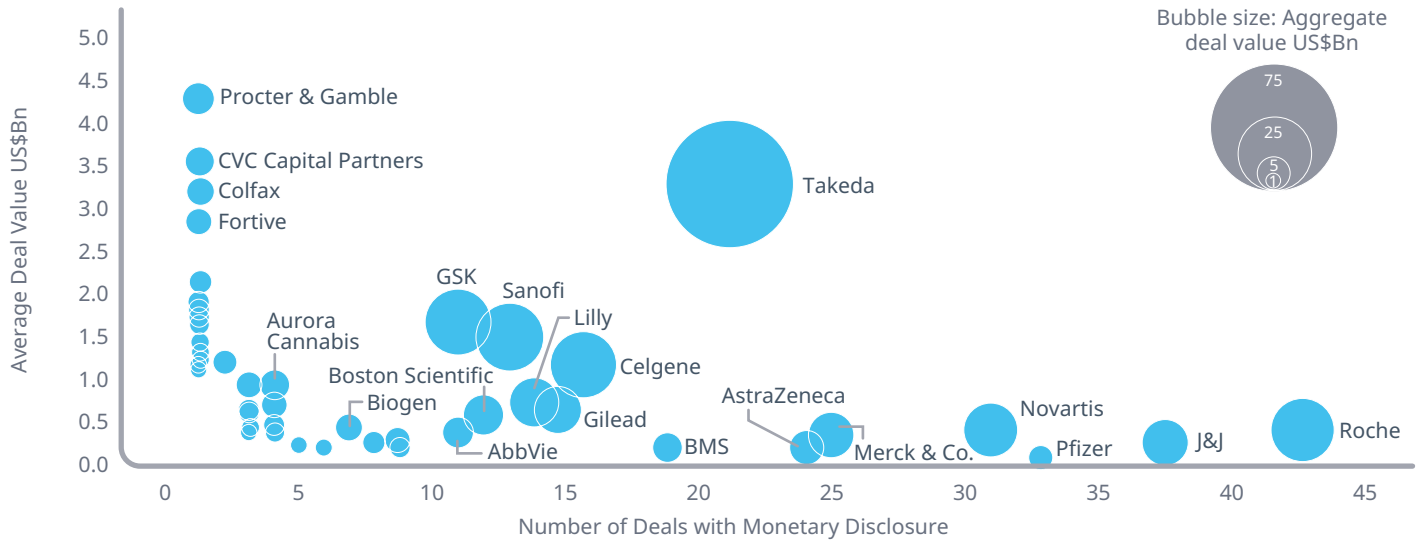
Exhibit 25: Top Mergers and Acquisition (M&A) Deals in 2018 Ranked by Total Deal Value

TOTAL DEAL VALUE	COMPANIES	DEAL DRIVER
£46 Bn ($62.3 Bn)	Takeda Pharmaceutical, Shire	Increased footprint in US market, expanded portfolios in neuroscience and gastroenterology, rare disease franchise
$13 Bn	GlaxoSmithKline (GSK), Novartis	Full ownership of consumer healthcare joint venture
$11.6 Bn	Sanofi, Bioverativ	Haemophilia franchise, rare disease pipeline assets
$9 Bn	Celgene, Juno Therapeutics	Cellular immunotherapy platform
$8.7 Bn	Novartis, AveXis	Phase III gene therapy for spinal muscular atrophy
$7 Bn	Celgene, Impact Biomedicines	Fedratinib, a Phase III Janus kinase 2 (JAK2) inhibitor for myelofibrosis
$5.1 Bn	GSK, Tesaro	Expanded oncology pipeline including Zejula® (niraparib), a selective poly ADP-ribose polymerase PARP) inhibitor
€3.9 Bn ($4.8 Bn)	Sanofi, Ablynx	Nanobody® technology platform, strengthened pipeline in rare blood disorders
€3.4 Bn ($4.2 Bn)	Procter & Gamble, Merck KGaA	Expansion of consumer health business
€3.03 Bn ($3.5 Bn)	CVC Capital Partners, Recordati	Growth in orphan disease and specialty care markets

Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

Deals announced in 2018 included 415 in-licensing or in-bound partnership agreements totaling $272 billion in agreed payments

Exhibit 26: Companies by Aggregate Value of All Disclosed Deals in 2018



Source: IQVIA. IQVIA Pharma Deals - Review of 2018. Mar 2019. Available from: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

- Large pharma continues to acquire or license assets between themselves and with EBPs. Of the 45 companies assessed, 415 deals were transacted in 2018, for an aggregate disclosed value of $272 billion.
- On average, companies carried out 9.2 deals each, with deals summing to an average of $6 billion per company, and the median deal amount at $2.6 billion.
- Takeda's acquisition of Shire was the largest deal, with Takeda spending $62 billion to acquire the rare disease-focused Shire.
- Roche and Johnson & Johnson were the most prolific deal-making companies, with 37 and 42 deals, respectively. However, their average deal values were $396 million and $239 million, some of the lower average aggregate deals seen.
- In contrast, GSK, Sanofi, and Celgene carried out fewer deals, with 11, 13, and 16, respectively, though average value per deals ranged from $1.1 to $1.6 billion. These differences between large companies reflect differing company strategy and business approaches.
- A small group of companies carried out a single deal each in 2018, though these deals were some of the largest. These include Proctor & Gamble's acquisition of Merck's consumer health business at $4.2 billion, and CVC Capital Partners acquisition of Recordati, a rare disease company, for $3.5 billion.
- Similarly, Colfax acquired DJO Global, an orthopedic company for $3.15 billion, and Fortive acquired Johnson & Johnson's advanced sterilization products business for $2.8 billion.

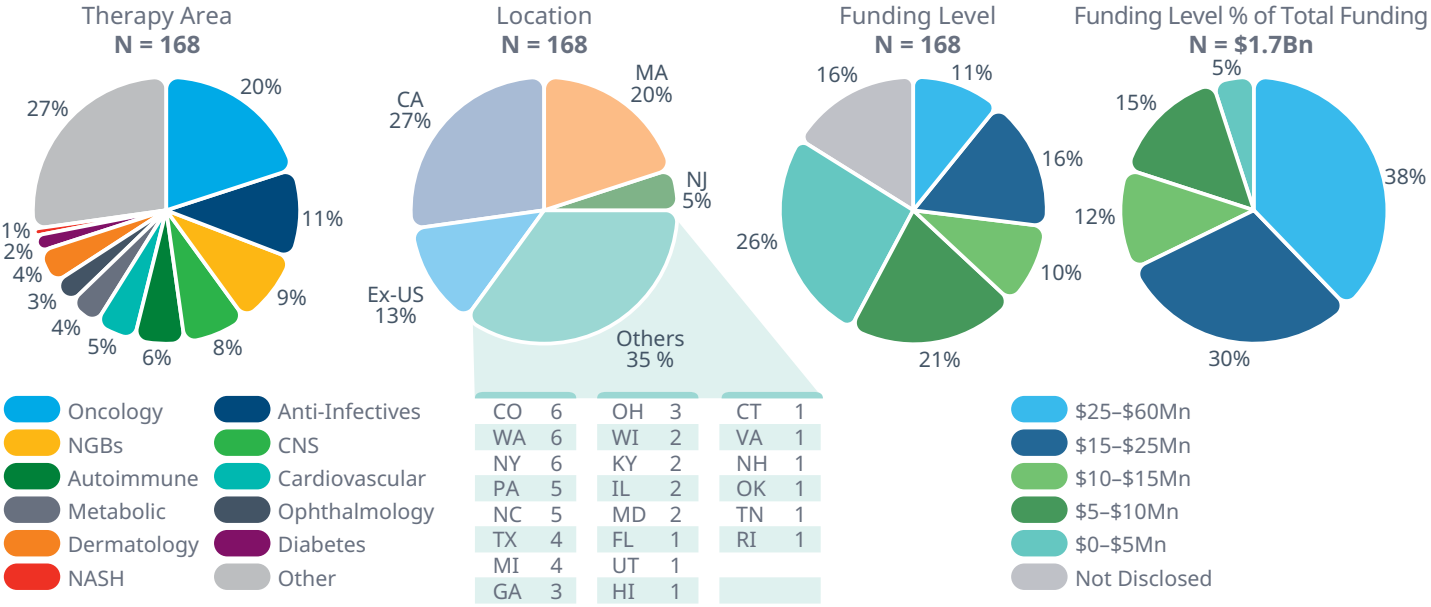
Chart notes: Disclosed deals excluding out-licensing deals and divestments by such companies are included. Number of deals includes some without disclosed deal-value and average deal value is the total disclosed value divided by all deals including those without disclosed value. For example, of the 21 deals involving Takeda, only seven had values disclosed in the public domain totaling $67.8 billion. Celgene and BMS are treated as separate companies and their expected merger excluded from this analysis, as the deal remains ongoing.

Profile of the 2008 Series A financing cohort

- Startups received funding in 2008 across a range of therapy areas, including high profile, including next-generation biotherapeutics, and at varied funding levels, with half occurring in three U.S. states
- The 168 companies received $1,685 million in financing in 2008, with 87% of that funding U.S.-based, and over half of the companies headquartered in either California, Massachusetts or New Jersey.
- Thirty-seven percent of the companies received more than $10 million in 2008, accounting for 80% of total funding.
- Ten years after initial financing, 51% of companies were privately held.
- Seventeen percent of the companies (28/168) have gone public within ten years of their initial funding, having received $413 million in initial financing and are now valued at over $14 billion.
- Of those twenty-eight publicly traded companies, five now have market capitalization of over $1 billion dollars.
- Forty-three companies have been acquired since initial financing; more than half by other emerging biopharma companies.
- Over half of financed companies have molecules in late-stage development.
- Some companies are focused on drug-discovery platforms, and have licensed the drugs resulting from the platform or partnered with other companies, demonstrating not all companies are focused on following assets from discovery to the market.
- Six drugs from five companies were approved within ten years of financing.
- Five of the six drugs have launched in the United States, all but one approved after May 2016.
- Two of these drugs have more than $100 million in 2018 sales were launched in 2014 and 2016, while the other drugs were launched more recently.

Startups received funding in 2008 across a range of therapy areas and at varied funding levels, with half occurring in three U.S. states

Exhibit 27: Companies Receiving Series A Financing in 2008 by Feature



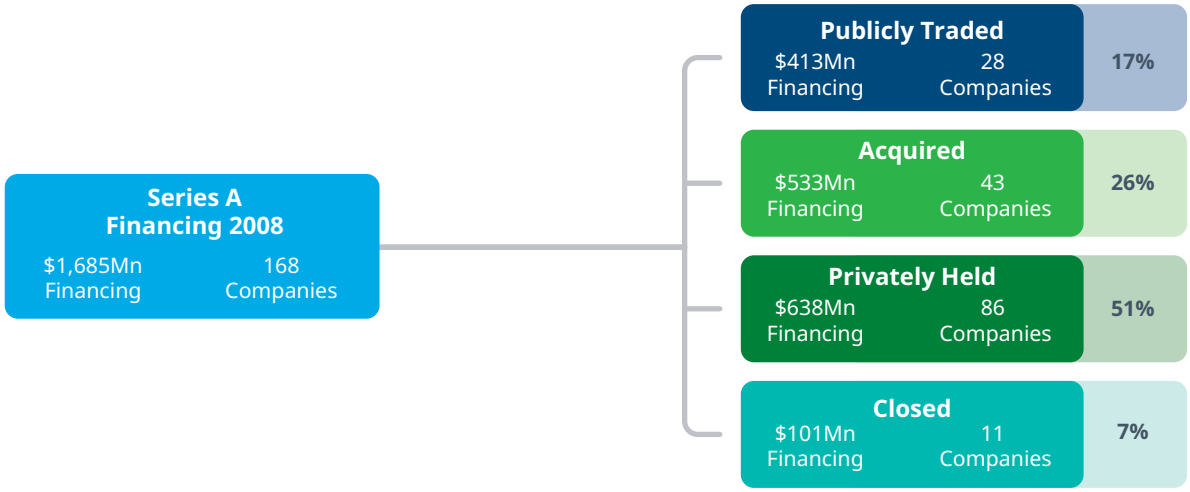
Source: BIO: Emerging Company Investment and Deal Trends, 2009-2018, May 2019; IQVIA Institute, May 2019

- The 168 companies that received Series A financing in 2008 were focused in a range of therapies, some of which have since become very high-profile, including Next-Generation Biotherapeutics like stem cells, gene therapy and RNAi technologies.
- The largest area of focus for these companies was oncology, mirroring its rise in importance to the overall pipeline since 2008.
- Two companies were focused in non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), an area with a significant ongoing research program in the broader industry.
- Over half of the companies are headquartered in either California, Massachusetts or New Jersey, with another 16 companies based in the northeast corridor from Maryland to New England.
- Other parts of the United States and the world have had less success in building investor interest in large numbers of startups, with only 13% of companies outside the United States.
- Companies received widely varying amounts of initial financing, with 37% of the companies receiving more than $10 million in 2008, but accounting for 80% of total funding.

Chart notes: CNS = Central Nervous System. Initial investment in Series A financing was identified for 168 companies receiving funding in 2008. Funding amounts were disclosed for 144 of the 168 companies and are included only for the initial financing in 2008. Two companies (Oceana and Lumavita) had received some funding and had approved products prior to 2008. Subsequent financing after 2009 has not been included. Therapeutic area of focus has been assessed based on the lead compound or platform at the time of financing.

Ten years after initial financing, 51% of companies were privately held

Exhibit 28: Initial Series A Financing in 2008 and Subsequent Company Structure/Ownership



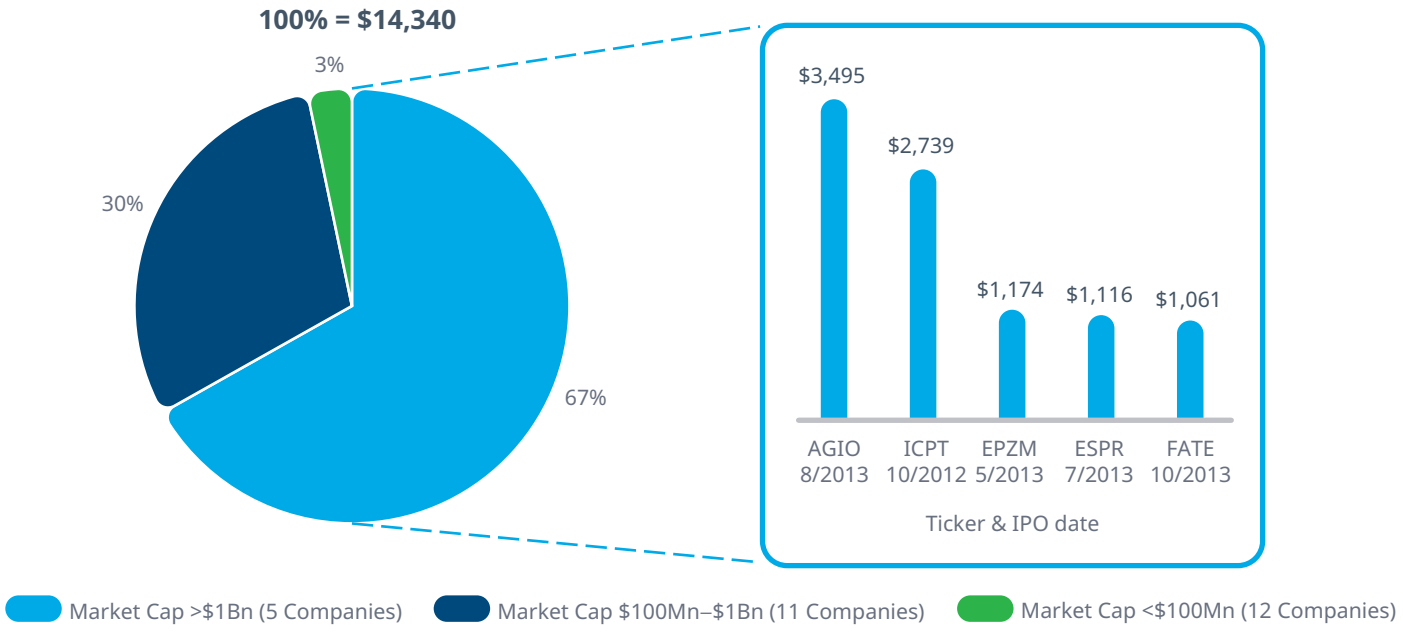
Source: BIO: Emerging Company Investment and Deal Trends, 2009–2018, May 2019; IQVIA Institute, May 2019

- Overall, 168 companies received $1,685 million in financing in 2008 or 2009, with 87% of that funding U.S.-based.
- Since the initial financing, 51% of companies are still privately held, 7%, or 11 companies have closed and 26% have been acquired.
- Twenty-eight companies (17%) have gone public within ten years of their initial funding, having received $413 million in initial financing and are now valued at over $14 billion.
- Forty-three companies have been acquired, 22 by other emerging biopharma companies and 14 by large pharma companies, though some of the assets that have changed hands in these transactions have subsequently failed in trials.
- Over half of the companies that received financing are still privately owned.
- Eleven of the 168 companies have closed, having failed to progress their research, or find a purchaser or funding streams to continue operations.

Chart notes: Initial investment in Series A financing was identified for 168 companies receiving funding in 2008. Funding amounts were disclosed for 144 of the 168 companies and are included only for the initial financing in 2008. Two companies (Oceana and Lumavita) had received some funding and had approved products prior to 2008. Subsequent financing after 2009 has not been included.

Twenty-eight companies are publicly traded, five of which now have market capitalization of over $1 billion dollars

Exhibit 29: Publicly Traded Companies and Their Current Market Capitalization $Mn



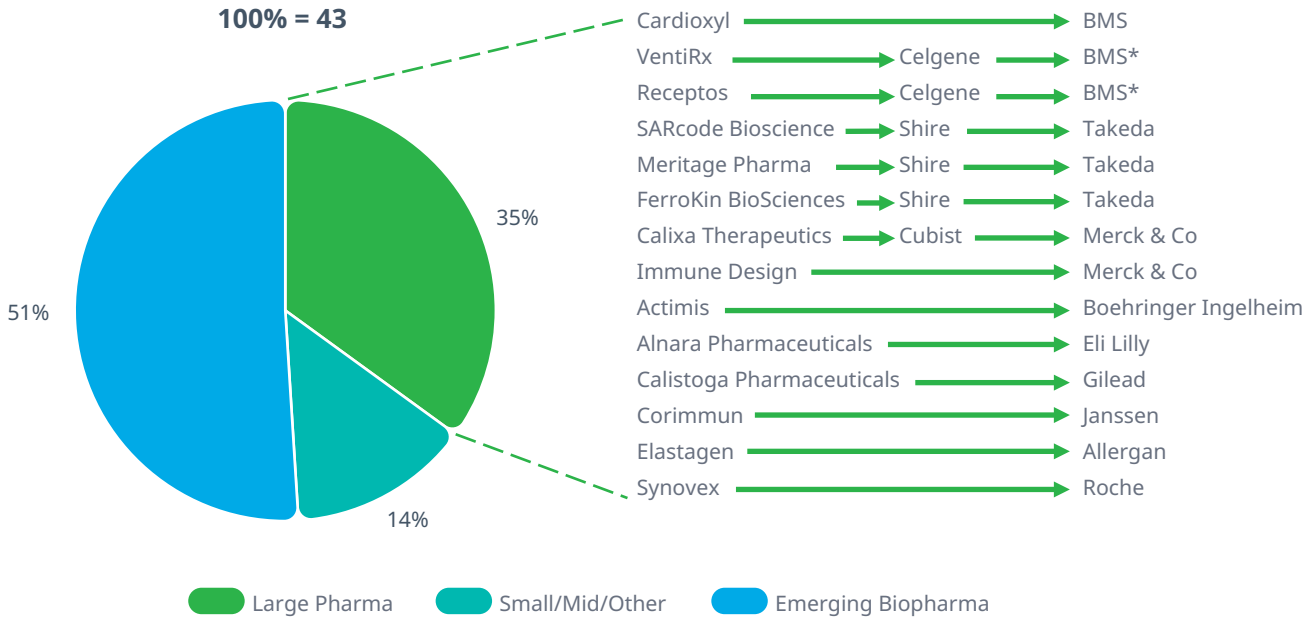
Source: BIO: Emerging Company Investment and Deal Trends, 2009-2018, May 2019; IQVIA Institute, May 2019

- Of the 28 companies that have gone public, the five with market capitalization above $1 billion all had IPOs between October 2012 and October 2013, and are now valued at over $9.6 billion.
- Agios is focused on precision medicines related to cancer metabolism in leukemia, including Tibsovo and Idhifa, two of the six drugs which have been subsequently approved from this group of companies.
- Intercept has a focus on non-viral liver diseases including NASH, NAFLD, primary sclerosing cholangitis (PSC) and biliary atresia, and has licensing partnerships for commercialization outside the United States.
- Epizyme focuses on epigenetics and has five molecules in development, and has partnerships with Celgene and GlaxoSmithKline.
- Esperion focuses on non-statin treatments for patients with elevated LDL (low-density lipoprotein, so-called bad cholesterol).
- Fate Therapeutics is an immunology company with a focus in cancer and other immune disorders with five programs in Phase I and eight in preclinical research.
- Eleven of the companies are now valued between $100 million and $1 billion, and 12 companies are collectively valued at $430 million.

Chart notes: Market capitalization values as of April 15, 2019. Initial investment in Series A financing was identified for 168 companies receiving funding in 2008 or continuing into 2009. Subsequent IPO has been identified for 28 companies.

Forty-three companies have been acquired since initial financing; more than half by other emerging biopharma companies

Exhibit 30: Acquired Companies by Segment of Acquiring Company



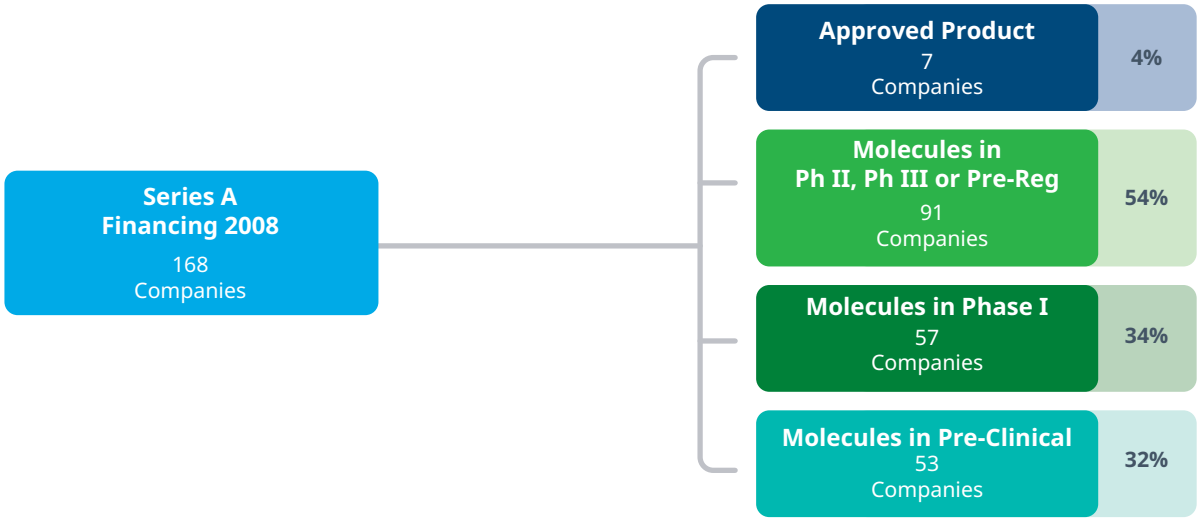
Source: BIO: Emerging Company Investment and Deal Trends, 2009-2018, May 2019; IQVIA Institute, May 2019

- Forty-three of the 168 companies have been acquired since their initial financing, more than half by another emerging biopharma and some of them multiple times. Large pharma companies have acquired 14 of the companies, five of them by three large companies that were themselves acquired by other large companies.
- BMS and Celgene acquired Cardioxyl, VentiRx and Receptos, focused in heart failure, solid tumors and a drug-discovery platform G protein-coupled receptor (GPCR) technology, respectively.
- Shire had acquired SARCode, Meritage and FerroKin prior to being acquired by Takeda. The treatments include dry eye, GI, rare diseases and an iron-chelator to address iron overload, common in patients receiving chronic transfusions.
- Merck has acquired Calixa and Immune design, the first through their Cubist purchase.
- Privately-held Boehringer Ingelheim purchased Actimis for their respiratory franchise in 2008, shortly after the initial financing.
- Eli Lilly's purchase of Alnara brought them liprotamase, a cystic fibrosis enzyme treatment, which they subsequently sold to Anthera. Development was recently discontinued after failing to reach a Phase III endpoint.
- Gilead has augmented their cancer portfolio with the purchase of Seattle-based Calistoga.
- Janssen acquired German Corimmun for their antibody and peptide-based cardiovascular treatments.
- Allergan added to their aesthetics portfolio with scar-remodeling and wound-repair treatments acquired with Elastagen.
- Roche acquired Adheron, the new name of Synovex, which has been focused on antibody treatments for inflammation by interrupting the cell surface protein CAD-11.

Chart notes: Initial investment in Series A financing was identified for 168 companies receiving funding in 2008. Subsequent acquisition has been identified for 43 companies, which have been grouped by company segments. * BMS acquisition of Celgene has been announced but the final closing is not expected until 3Q 2019.

Over half of financed companies have molecules in late-stage development

Exhibit 31: Portfolio Evolution Since initial Financing



Source: BIO: Emerging Company Investment and Deal Trends, 2009-2018, May 2019; IQVIA Institute, May 2019

- Five companies have approved products within ten years of their initial financing, one (Agios) with two products. Two other companies already had approved drugs prior to getting their financing in 2008 (Oceana and Lumavita).
- More than half of the 168 companies now have compounds in late-stage research.
- Two-thirds of the companies have early-stage research ongoing, with some continuing their initial projects, and others pursuing additional developments begun after funding was received.
- Some companies are focused in drug-discovery platforms. They have licensed the drugs resulting from the platform, or partnered with other companies to develop those assets, while continuing to engage in early drug discovery. In this way, not all companies are focused on following assets from discovery to the market.

Chart notes: Companies with approved products (7) includes Oceana and Lumavita, which had approved products prior to receiving financing in 2008. Companies may have products at multiple phases of development and segments are overlapping.

Six drugs from five companies were approved within ten years of financing

Exhibit 32: Approved Products

BRAND (MOLECULE)	INDICATION(S)	ORIGINAL COMPANY	APPROVAL DATE	REPORTED NET SALES (2018)
Apadaz (benzhydrocodone / acetaminophen)	Attention-deficit/hyperactivity disorder	KemPharm Inc.	Feb 2018	Launch expected 2H 2019
Ocaliva (obeticholic acid)	Primary biliary cirrhosis	Intercept Pharmaceuticals Inc.	May 2016	$177.8 Mn
Tibsovo (ivosidenib)	Acute myeloid leukemia	Agios Pharmaceuticals Inc.	Jul 2018	$13.8 Mn
Idhifa (enasidenib)	Acute myeloid leukemia	Agios Pharmaceuticals Inc. (Celgene has worldwide development and commercialization rights)	Aug 2017	$68 Mn
Xerava (eravacycline)	Multidrug-resistant infection	Tetraphase Pharmaceuticals Inc	Aug 2018	$0.2 Mn
Zydelig (idelalisib)	Chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma and follicular lymphoma (FL)	Calistoga Pharmaceuticals Inc.	Jul 2014	$133 Mn

Source: BIO: Emerging Company Investment and Deal Trends, 2009-2018, May 2019; IQVIA Institute, May 2019

- There have been six drugs approved from this group of companies and products, all at least six years after financing and in a substantially faster timeframe than other drugs.
- Five of the six drugs have launched in the United States, all but one approved after May 2016.
- The two drugs with more than $100 million in 2018 sales were launched in 2014 and 2016, while the other drugs were launched more recently.
- Ivosidenib (Tibsovo) was approved in July 2018, but not launched in the United States until October, and achieved $13.8 million in 2018 sales in 2.5 months.
- Eravacycline, for multidrug-resistant infections, should be used rarely and has had a similar 2.5 months of sales since launching, achieving $0.2 million in sales.

Chart notes: Excludes Delfux from Oceana and Femifect from Lumavita, which were approved and launched prior to the companies receiving financing in 2008.

Looking ahead

- 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.
- 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, which extrapolated how these eight drivers of change would impact the effort, success and productivity of trials in the next five years.
- The number of drugs in active late-stage clinical development has increased 39% over the past five years, reflecting the increased level of investment in scientific innovation and raising the level of competition in key therapy areas at the same time. Looking ahead, a number of trends are expected to drive changes in the way EBPs conduct clinical development.
- 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 improvement in effort of 11%.
- Emerging biopharma companies assessing commercialization options and strategies for their assets will be facing a large and dynamic global market for medicines designed for unmet patient needs.
- Emerging biopharma companies will have many choices across various areas, including big data and artificial intelligence, to support and explore how they relate to their new medicines. Rather than divide their resources, many view partnerships as the way to adapt to these environmental and generational shifts.

LOOKING AHEAD

Over the next five years, EBPs engaged in R&D and commercialization (directly or indirectly) will face a changing environment and need to adapt accordingly. These changes include trends that are reshaping clinical development, as well as trends affecting the commercialization of medicines. In addition, the financing and deal-making ecosystem in which companies decide to license, buy or sell, or partner on assets will transform. As some companies adapt to events more rapidly and with greater affinity for the critical factors that will drive success, they will outperform. Others will be better able to maximize value through their understanding of the world in which the purchasers of their assets operate.

CLINICAL DEVELOPMENT

The number of drugs in active late-stage clinical development has increased 39% over the past five years, reflecting the increased level of investment in scientific innovation and raising the level of competition in key therapy areas at the same time. Looking ahead, a number of trends are expected to drive changes in the way EBPs conduct clinical development (see Exhibit 33).

These include the ongoing revamping of the regulatory landscape, which has added new breakthrough designations in recent years, as well as allowing regulators in the United States and other geographies the latitude to make decisions based on less information, especially in the case of life-threatening or rare diseases. Additionally, regulators may now assess real-world evidence, or include patient reported outcomes (PROs) in their decision-making. The expansion of the genomic revolution is now driving the development of more drugs informed by biomarker tests, which further result in optimized trial design and development in the presence of pre-screened pools of patients. Biomarkers continue to be discovered, both as a result of drug discovery and through other research, and the wider range of tests and their availability will significantly enhance all aspects of drug development. The uncertainties surrounding patient population size and targeting, which often confound developers and marketers, are becoming more surmountable through the use of real-world data, predictive analytics and AI, and the interactive effects of a number of other advances.

Companies which adopt digital health technologies will range from those who use technology to enhance clinical development, patient experience, commercial operations efficiency as well as safety and compliance. The use of mobile apps in trials can help companies engage with trial participants in a more integrated and holistic way, retaining trialists despite potential challenges and enhancing trial speed while reducing costs. Digitally collected patient-reported outcomes are increasingly a way to optimize trial information, and in some trials have improved overall survival; in cancer trials, treatment escalations were able to be made more swiftly, improving trial outcomes.

In examining these key trends, all are expected to yield improvements in trial success rates, however, increases in productivity will additionally be driven by decreases in trial complexity and duration (i.e., reductions in effort), resulting from most trends. 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, resulting from the largest percentage drop in effort (-12%) and an 18% increase in success. While predictive analytics and PRO are among the trends which 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 yet the largest increases in effort.

Eight key trends are driving change in clinical development

Exhibit 33: Trends Driving Change in Clinical Development

Digital health technologies, still immature, will require significant investment to deliver their full potential. EBP companies may benefit from these technologies as they continue to evolve – likely through the use of outsourced clinical operations or alongside a larger development partner more likely to invest in these new technologies. Assessing the value and potential of digital technologies related to a specific development program could be a critical success factor when assessing trial outsourcing or partnerships.

Increased focus on PROs will shed new light on patient outcomes (PROMs) and experience (PREMs) outside the clinical setting to inform ongoing clinical decisions, serve as secondary endpoints, influence labeling, and accelerate trial times. A large proportion of EBP launches are in areas much more commonly associated with PROs, where patient experience and function are impacted or the delivery system, convenience or tolerability might offer a key differentiator, but only if supported by a patient measures.

Real-world data is increasing exponentially in volume and complexity, but its use requires significant investment. To participate and benefit from these changes, smaller companies may need to find a partner or vendor able to integrate these approaches, but the impact could be transformative if pursued. It may accelerate trials by aiding in investigator/site selection, help optimize trial design including right-sizing trials for treatment effect, and enable new trial designs.

Predictive analytics and AI offer the potential to radically reduce costs across the biopharmaceutical enterprise, but leveraging these new technologies is a large investment and may not be core to the founding principles of a science-based startup. EBP companies that can find applications closely aligned to their research mission may reap significant advantages, and see increased probability of success and approval. For trials, these tools will identify new clinical hypotheses to test, reduce trial design risks, speed enrollment by identifying protocol-ready patients, and help narrow trial patient populations to pre-defined subgroups (i.e., precision medicine). It will also enable adaptive designs that lead to earlier approval with smaller patient samples.

Shifts in drug types include the development of targeted therapies and Next-Generation Biotherapeutics will improve efficacy and success rates overall and lead to trials for new indications lacking current options, and 92% of the current crop of late-stage development in these next-generation areas are EBP companies. As many of these therapies have short treatment durations, and some have shown curative results, costs are expected to be high, as is payer concern about overall costs. EBP companies will be reaching the end of their development journey with key questions about how best to commercialize their assets.

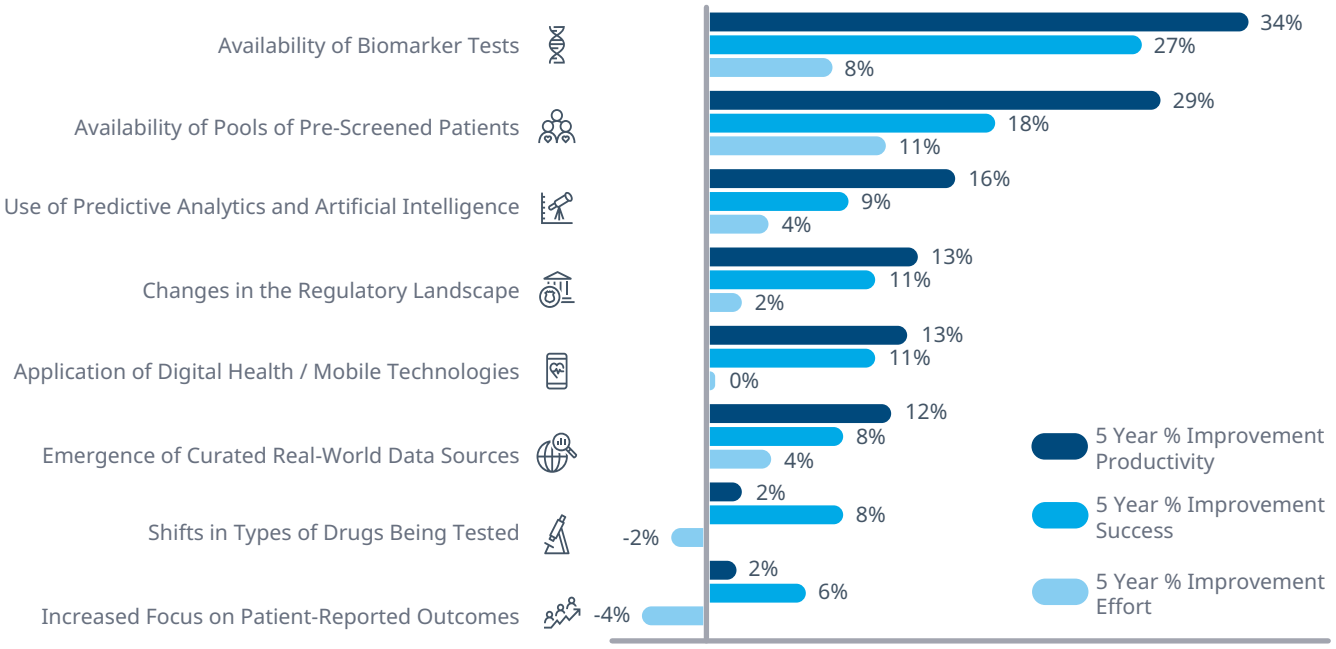
Increased availability and ease of biomarker testing is core to the research focus of a whole range of EBP companies and has been a democratizing force enabling these startups to continue to develop their assets for longer periods prior to eventual sale or licensing. It has also been a key driver increasing the value of some assets where the benefit to a patient subpopulation is much more directly assessable.

Availability of pools of pre-screened patients and direct-to-patient recruitment will facilitate trial recruitment and help sites/trials hit accrual targets, but the investment in building these pools may mean that EBP companies struggle to compete with better funded rivals. While these pre-screened pools are projected to be one of the larger factors driving better clinical development productivity in the future, access to the pools may be more limited and come at the cost of surrendering an asset to a larger partner.

Changes in the regulatory landscape will encourage the use of biomarkers and further precision medicine, drive use of novel trial designs and endpoints, and provide means for accelerated drug approvals. It may also minimize work burden through the use of risk-based monitoring, electronic records, and electronic signatures and speed drug approvals by increasing the use of real-world data to expedite drug development, especially for drugs pursuing an unmet medical need indication. While some of these approaches require a base level of competence, increasingly emerging companies are taking advantage of this newer regulatory flexibility to bring their drugs to market and in some cases shorten the gap between EBPs and better funded larger companies.

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

Exhibit 34: Predicted Percentage Change in Productivity, Effort and Success per Trend from 2018 to 2023



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

Several other factors are reshaping approaches to clinical development with the potential to improve productivity – defined as success rates divided by trial complexity and duration – from current levels. Some types of drugs will be more challenging than others to develop, and drive an increase in 'effort' – defined as complexity and duration – similar to attempts to incorporate more PROs into trials (see Exhibit 34).

Larger pharma companies have greatly advanced their focus on many of these issues, as they develop and market many more drugs than smaller companies and often have large internal infrastructures and resources. Smaller companies are often deciding which functions are absolutely critical to their company as they grow, meaning prioritizing resources to address a future trend is often beyond their means. However, emerging companies can still benefit from the awareness of these trends, particularly as they could affect the valuation of their assets when negotiating a licensing deal, company sale or partnership.

The types of therapies driving much of the deal-making and asset-valuation in recent years have been shifting from targeted oncologics to cell and gene therapies and other next-generation biotherapeutics. The speed of development of some of these treatments could radically alter the landscape for companies with a marketed product, either potentially diminishing or reinforcing the advantage of incumbent products and companies. How the first-mover develops relationships in a crowded market and maintains that advantage over time is a critical factor concerning all companies, and ultimately influences many of the negotiations around emerging companies and products. If a gene-editing technology can be developed and approved in a few years, which may well be the case over the next decade, it will have broad implications for the companies marketing therapies in

that disease, as well as insurers, providers and patients. Curative treatments have been relatively rare historically, but in the past ten years several transformative and tolerable treatments have become available, often with cure in short or even single dosing regimens.

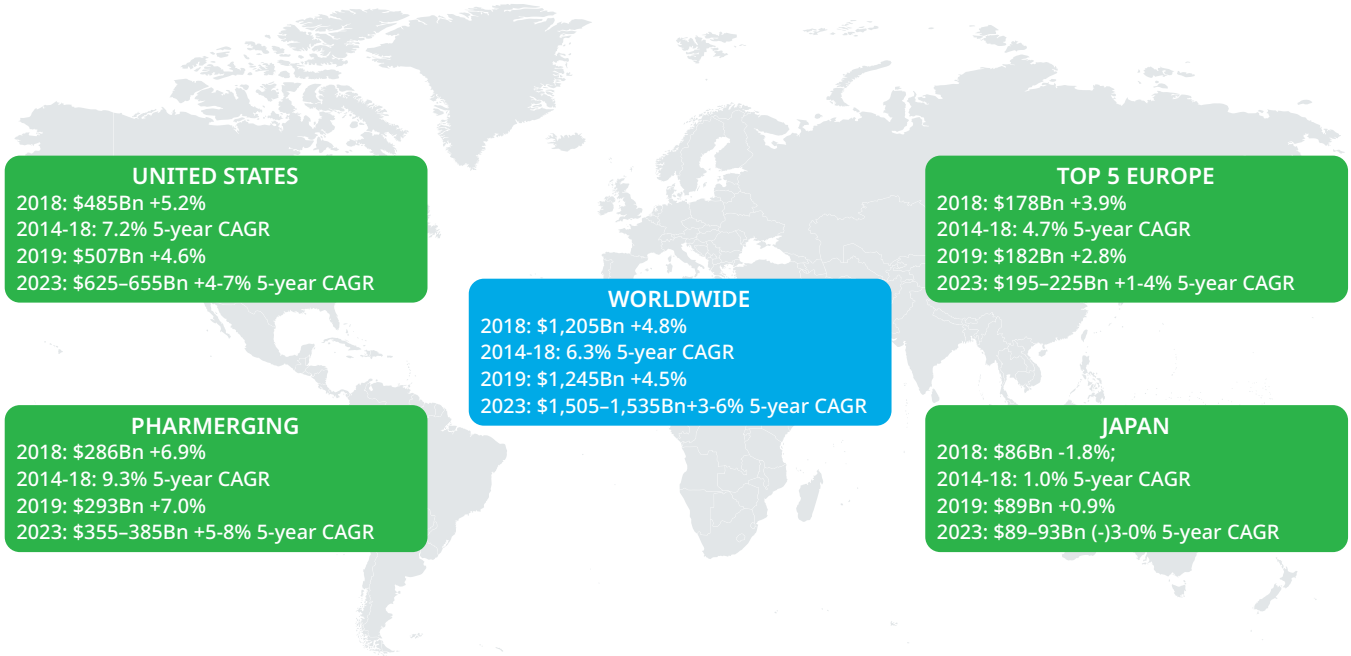
These kinds of treatments are expected to be more common in the near future and promise transformation of their target diseases and the funding arrangements affecting all drugs.

In a future where payers are making complex tradeoffs, marginally beneficial late-to-market products of only modest incremental clinical benefit will lead to a different and more challenging commercialization roadmap. A large number of drugs developed have offered incremental improvements; coupled with the coming increase in commercialization challenges for such products, there will be a significant change in the risk profile of all launches. Understanding these shifting dynamics, the competencies necessary to navigate them and the true value of a compound, biologic or process may not be a single learning process, but an ongoing one marked by building consensus between investors, partners, and market stakeholders. An emerging company solely focused on the science and the clinical aspects of their drug may be ill-prepared to address these issues.

COMMERCIALIZATION

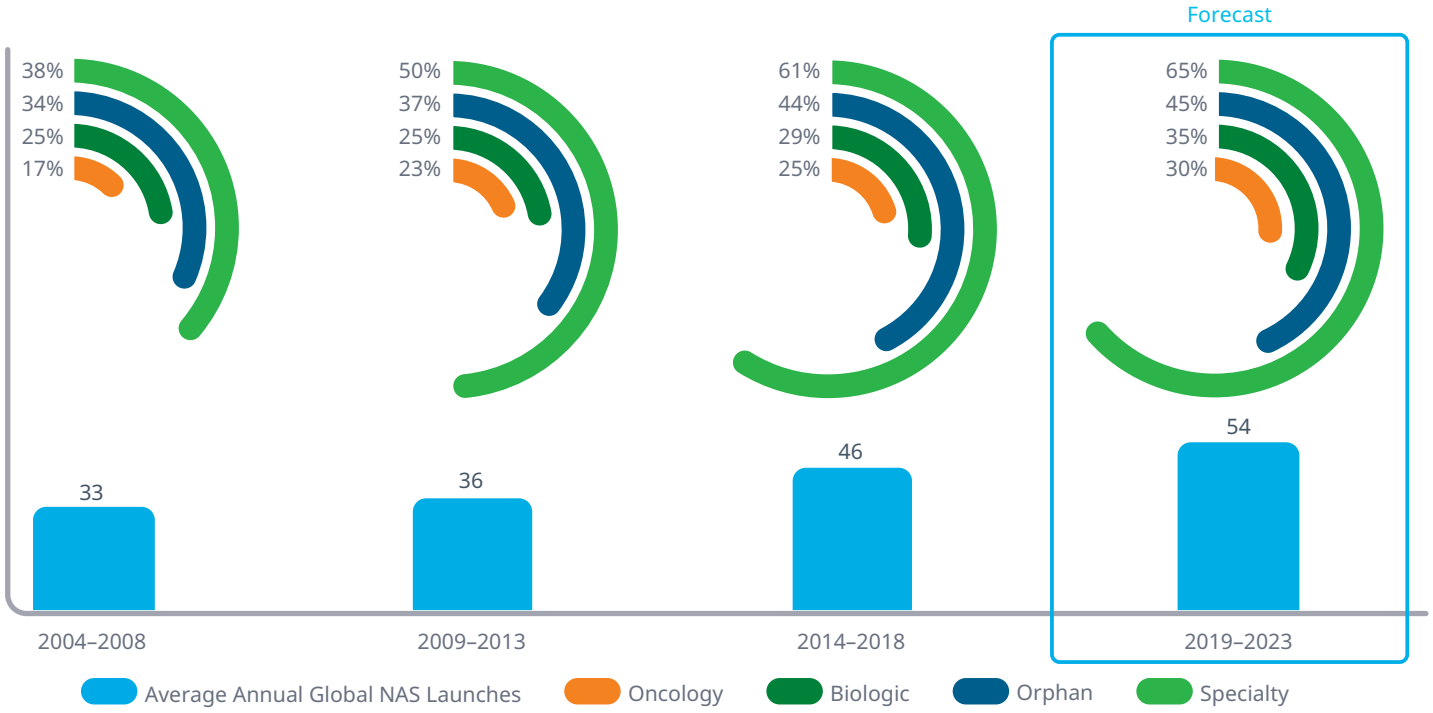
Emerging biopharma companies assessing commercialization options and strategies for their assets will be facing a large and dynamic global market for medicines designed to meet unmet patient needs. Over the next five years, the global demand for medicines is expected to continue to grow, both in in volume through expanded access and insurance coverage, and due to the continued flow of innovation and the use of newer treatments. Spending globally is expected to exceed $1.5 trillion in 2023, adding $50-60 billion per year in global spending, with half driven by large developed economies and a large proportion from novel medicines (see Exhibit 35).

Exhibit 35: Global Medicine Spending and Growth in Selected Regions, 2018–2023



Source: IQVIA Market Prognosis, Sep 2018; IQVIA Institute, Dec 2018

Exhibit 36: Average Number of Global NAS Launches Annually per Period and Percentage of Launches by Type



Source: 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

Many developed countries have targeted slowing healthcare spending growth as a key priority, and as a result the continued flow of new drugs presents a funding challenge for those health systems (see Exhibit 36). Existing mechanisms to adjudicate value range from negotiation of prices through insurers to the use of health technology assessments (HTA), which generally result in pressure on companies commercializing new drugs. These are becoming particularly important, as a small but growing group of products with extremely high prices for relatively few patients are reaching the market (see Exhibit 37). This also creates opportunities to deliver value through different formulations addressing unmet needs in smaller and sometimes lower-priced niches.

Across a range of therapy areas there is an increasing number of companies aspiring to develop and commercialize new treatment options, which will be supported by both sustained success rates and increased pressure, as stakeholders use the presence of multiple options to generate leverage in negotiations. As larger companies have recognized the need for assets in certain areas, the last few years have seen a frenzy of deal-making activity around immune-oncology therapies, cell and gene therapies and others. Alongside this trend, larger companies have been making lower overall up-front payments, while total licensing deal values have been relatively stable. Faced with less appealing offers for their assets and with financing available, more emerging companies are choosing to finish the development and commercialize their assets on their own.

KEY ENABLERS

In the next five to ten years, three key enablers will be important for EBPs to embrace to assure their success: the use of data and analytics, the adoption of technology and a critical need to employ flexible business models.

a) Data and analytics applications

The combination of technological advances, a decline in the cost of computing power and a generation of data scientists coming of age is creating and uncovering dramatic improvements in the quality and efficiency of clinical development and commercial operations.

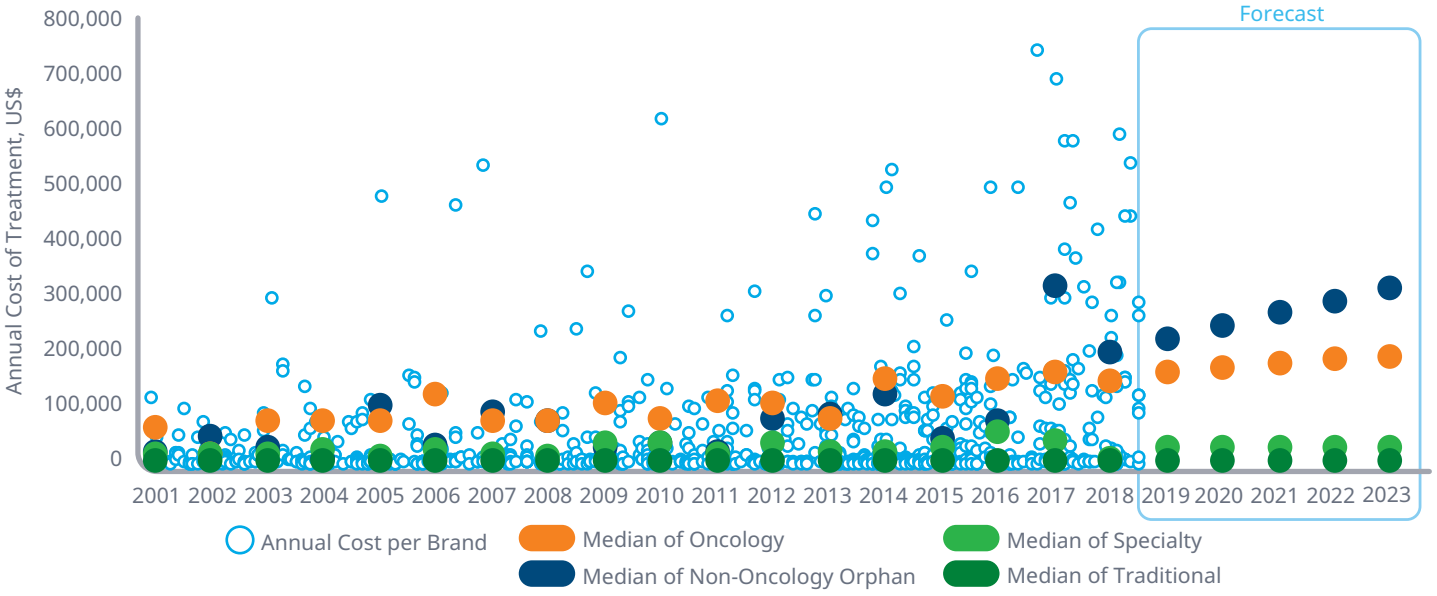
Companies are using advanced analytic models to identify and model candidates in drug discovery, to harmonize and integrate unstructured data in multiple languages, as well as optimize pattern recognition and accelerate the findings from early research. When artificial intelligence and machine learning are applied to the practical and logistical considerations of clinical trial operations, site selection, patient stratification, and managing trial costs can all be improved dramatically (see Exhibit 38).

b) Technology applications

Engaging with patients or consumers "where they are" is an increasing refrain in modern healthcare, as it is in modern consumerism. In both cases, patients are increasingly existing in a digital and connected world. By engaging with patients digitally, through e-mail, smartphones and apps and by collecting necessary health information in optimal ways enabled by these newer technologies, more information is being received from more patients, potentially increasing our knowledge and understanding of diseases.

These digital engagements can drive short-term and relatively easy successes, like efficiency gains and drug adherence improvements, but they suggest so much more is possible. The FDA has already approved therapies that use an app to encourage behavior change, and there will

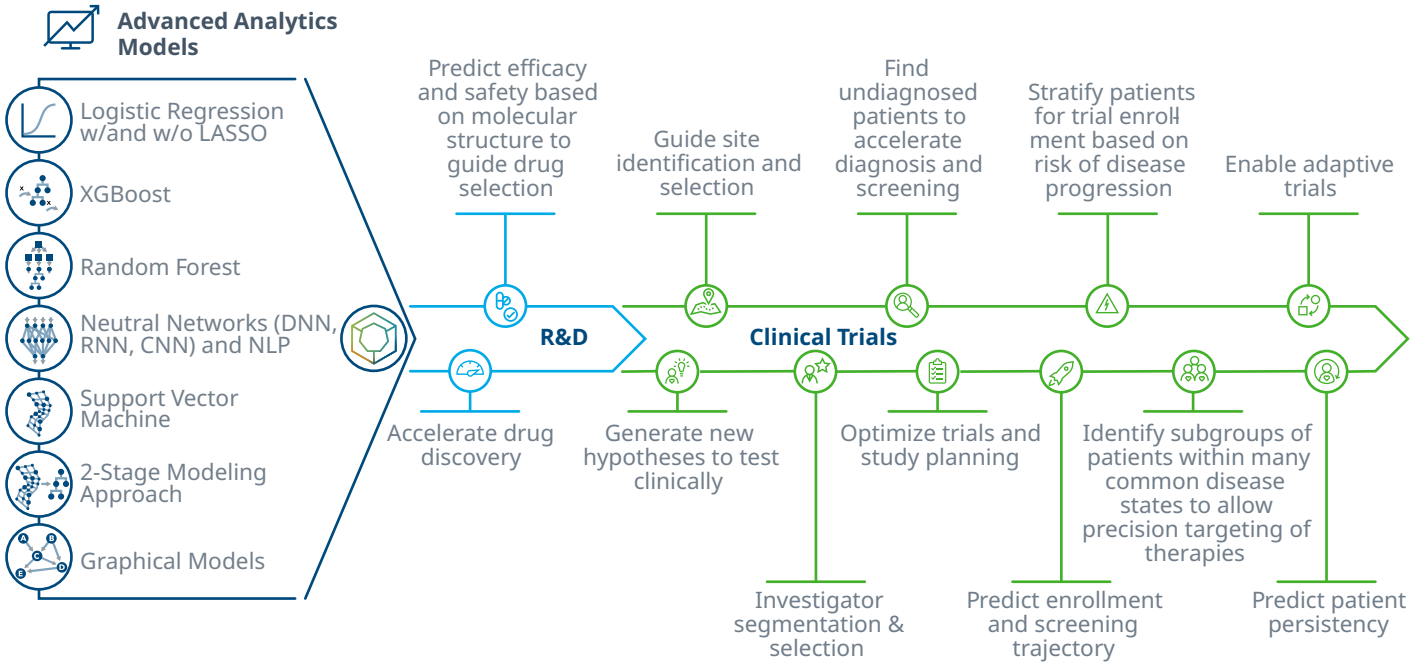
Exhibit 37: Annual and Median Costs of U.S. Brands by Type and Launch Year US$



Source: IQVIA National Sales Perspectives, Dec 2018; IQVIA Institute, Mar 2019

Chart notes: Annual costs based on invoice prices, with overall invoice-level spending divided by estimated numbers of patients. Patient estimates are based on audited volumes assuming all patients use the drug according to the approved label. Products are included in medians based on segment assignments. Oncology includes both orphan and non-orphan products. All other products that have orphan indications are grouped together and some products have both orphan and non-orphan indications in this group. Specialty and traditional products exclude orphan or oncology products but are otherwise defined according to IQVIA definitions. Projected median costs are based on simple extrapolation of the medians in the prior ten years.

Exhibit 38: Predictive Analytics and Artificial Intelligence Driving Value for Clinical Development



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

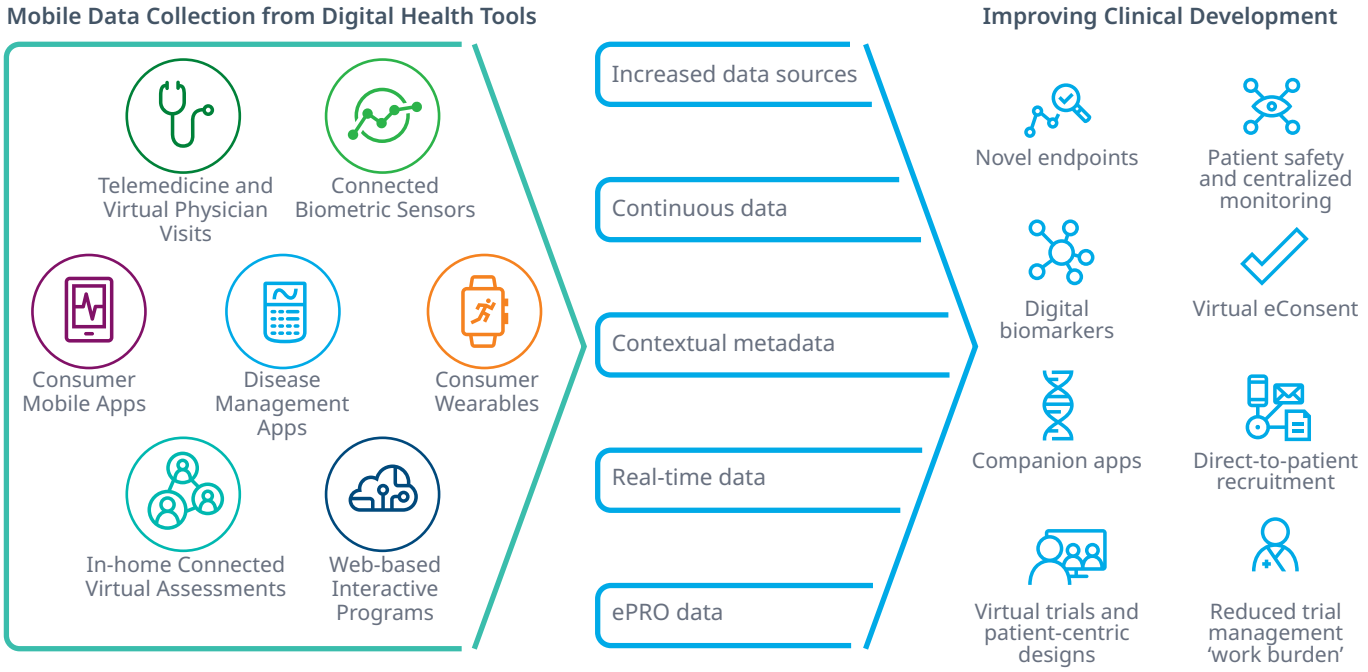
be many more areas of research exploring the potential of apps as therapies or in combination with drugs as combined therapies. Improved patient engagement in clinical trials with the potential for site-less trials and improved safety monitoring are also being explored (see Exhibit 39).

Emerging biopharma companies will be overwhelmed with choices of the areas to support and explore how they relate to their new medicines. Rather than divide their resources, many view partnerships as the way to adapt to these environmental and generational shifts. Those with potential therapies most affected by some of these trends can take advantage of their awareness to see value where others have not. As some drug therapy areas are saturated with older and generic treatments, the threshold for innovation to be accepted in the market approaches impossible levels; but a new imagining of therapeutic benefit, perhaps involving an app or a device, could be a unique value proposition only an outsider could see.

c) Flexible business models

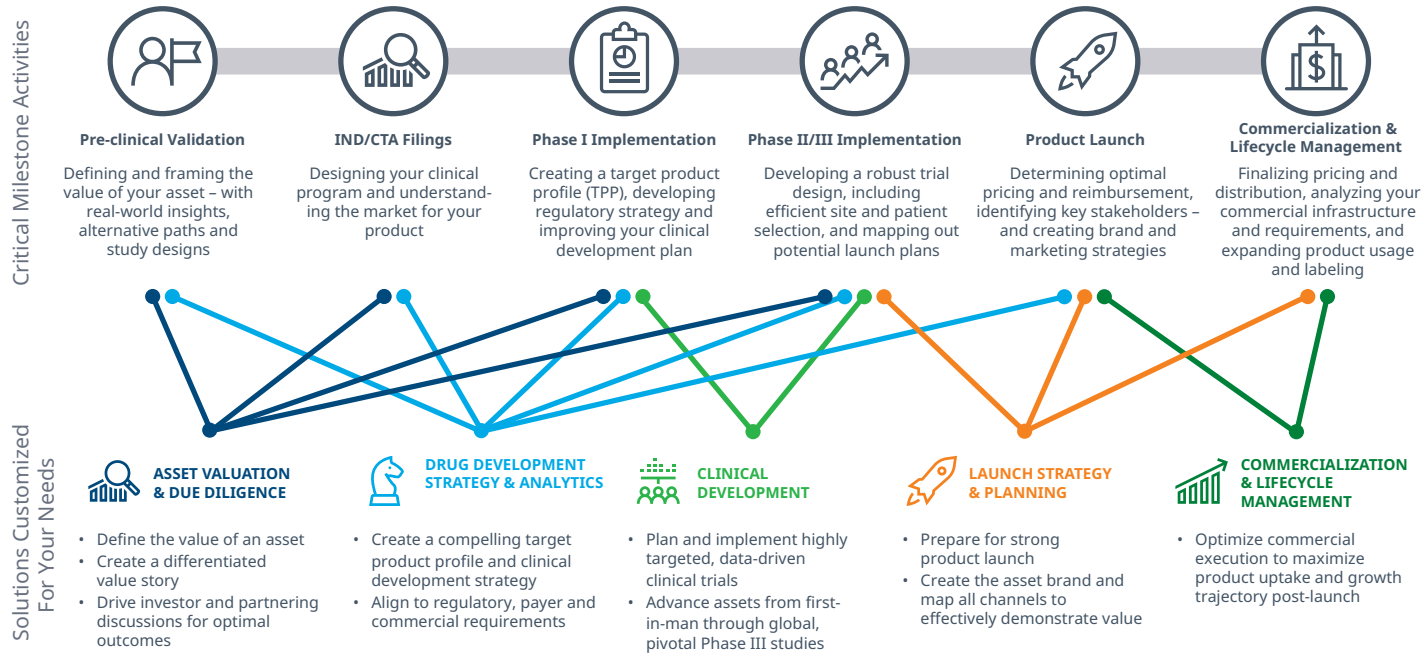
As emerging companies plan for the future, they can adapt a flexible commercial model, with contracts with partners, vendors and service providers which can be switched on or off as events dictate. A single compound's regulatory setback can prompt a derailing few months of reorganization, cuts or even the closing of the company. A more modular and flexible model would only scale up once the success was confirmed. This flexible approach has been more aspiration than reality for many companies because the technology, analytics, and integration necessary to manage such a complex enterprise simply could not be managed this way even a decade ago. As companies increasingly explore such structures, it becomes possible for more companies to develop and market an asset while handing over less of the potential return to other companies. In some cases, even just the plausibility of going alone may be a useful negotiating tactic in the sale of an asset (see Exhibit 40).

Exhibit 39: Digital Health Applications Transforming Clinical Development



Source: IQVIA Institute. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. Apr 2019. Available from: www.iqviainstitute.org/researchanddev2019

Exhibit 40: Advancing Asset Value Across Milestones



Source: IQVIA Biotech

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

IQVIA Patent Intelligence™ is a database of biopharmaceutical patents or equivalents in over 130 countries and including over 3,000 molecules. Research covers approved patent extensions in 51 countries, and covers all types of patents including product, process, method of use and others.

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

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.

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

Useful resources

IQVIA Pharma Deals Review of 2018

This Review provides an insightful overview of deal activity in 2018, as well as the outlook for deals in 2019. Key information provided includes the following:

- Top M&A and partnership deals in 2018
- Deal activity rankings of the top pharmaceutical companies
- Deal activity by therapeutic area and development phase
- Deal value analysis of M&A, licensing and R&D deals

Key highlights:
Deal activity in the life sciences sector slowed in 2018, as political uncertainty, leadership changes and changing regulatory and pricing landscapes took a toll. As was the case in 2017, small companies had various financing options available to them resulting in inflated company valuations, which thereby discouraged pharmaceutical companies from certain types of dealmaking.

Download at: https://www.iqvia.com/library/white-papers/iqvia-pharma-deals--review-of-2018

Launch Archetypes: The Bedrock of Successful Launch Strategies

From the moment that commercial planning begins, new product launches face a gauntlet of challenges to which many succumb. In fact, over half fail to meet financial expectations based on a broad internal analysis.

Brand teams can improve their chances of success in such a high-risk environment by understanding their product's Launch Archetype, as defined by the mix of unmet need in the market and the product's level of differentiation.

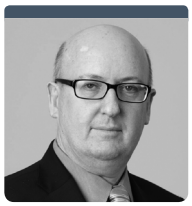
The **IQVIA Launch Center of Excellence** applies a proprietary scoring model along these two dimensions to all new product launches and, consequently, has identified four Launch Archetypes. This white paper discusses how marketers can develop successful launch strategies by studying other marketed products that share the same Archetype. It also provides perspective of the current launch environment through the lens of Archetypes, highlighting trends and the relationship between Archetype and market performance. Each Archetype comes with its own set of considerations, marketing implications, and associated launch challenges.

Download at: https://www.iqvia.com/locations/united-states/library/white-papers/launch-archetypes-the-bedrock-of-successful-launches

Definitions

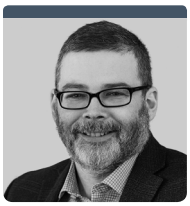
- **Early-stage pipeline** is defined as the developmental stages of discovery, preclinical, and Phase I.
- **Late-stage pipeline** includes developmental stages of Phase II, Phase III, pre-registration, and registration.
- **Next-Generation Biotherapeutics** are defined as cell, gene and nucleotide therapies.
    - Mechanisms include: 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 therapies

About the authors



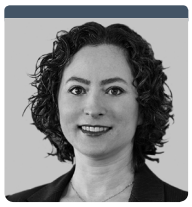
MURRAY AITKEN
Executive Director, IQVIA Institute for Human Data Science

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



MICHAEL KLEINROCK
Research Director, IQVIA Institute for Human Data Science

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



DEANNA NASS
Director of Publications, IQVIA
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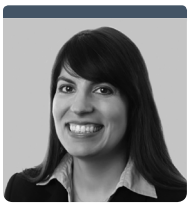
Deanna Nass is the director of publications at the IQVIA Institute for Human Data Science. She manages the development and production lifecycles of IQVIA Institute reports and performs analyses of global biopharmaceutical and healthcare trends. With a diverse background that spans from consulting and business development to market analysis and writing industry publications, she brings a unique perspective of the biopharma industry to the Institute. Deanna joined the Institute in 2013 and IMS Health in 2004. Deanna holds a B.A. in Biology from Yale University with a specialization in Neurobiology and a Certificate in International Affairs from New York University.



ALANA SIMORELLIS
Publications Manager, IQVIA
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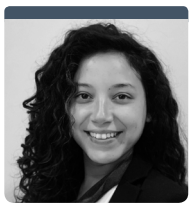
Alana is Publications Manager for the IQVIA Institute and helps manage aspects of IQVIA Institute research projects and publications, as well as conducting research and analysis within global healthcare. Alana came to IQVIA in 2016 having previously worked at Decision Resources Group for over six years as a Principal Business Insights Analyst. At Decision Resources group, Alana authored a number of publications within multiple disease areas that included Alzheimer's disease, pain, bipolar disorder, schizophrenia and major depression. Alana has a Ph.D. in Chemistry from the University of Utah and completed a postdoctoral fellowship at Brandeis University, where part of her research involved structural investigation of a protein associated with Parkinson's disease.



ELYSE MUÑOZ
Thought Leadership Manager, IQVIA Institute for Human Data Science

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

About the Institute

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

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

Research Agenda

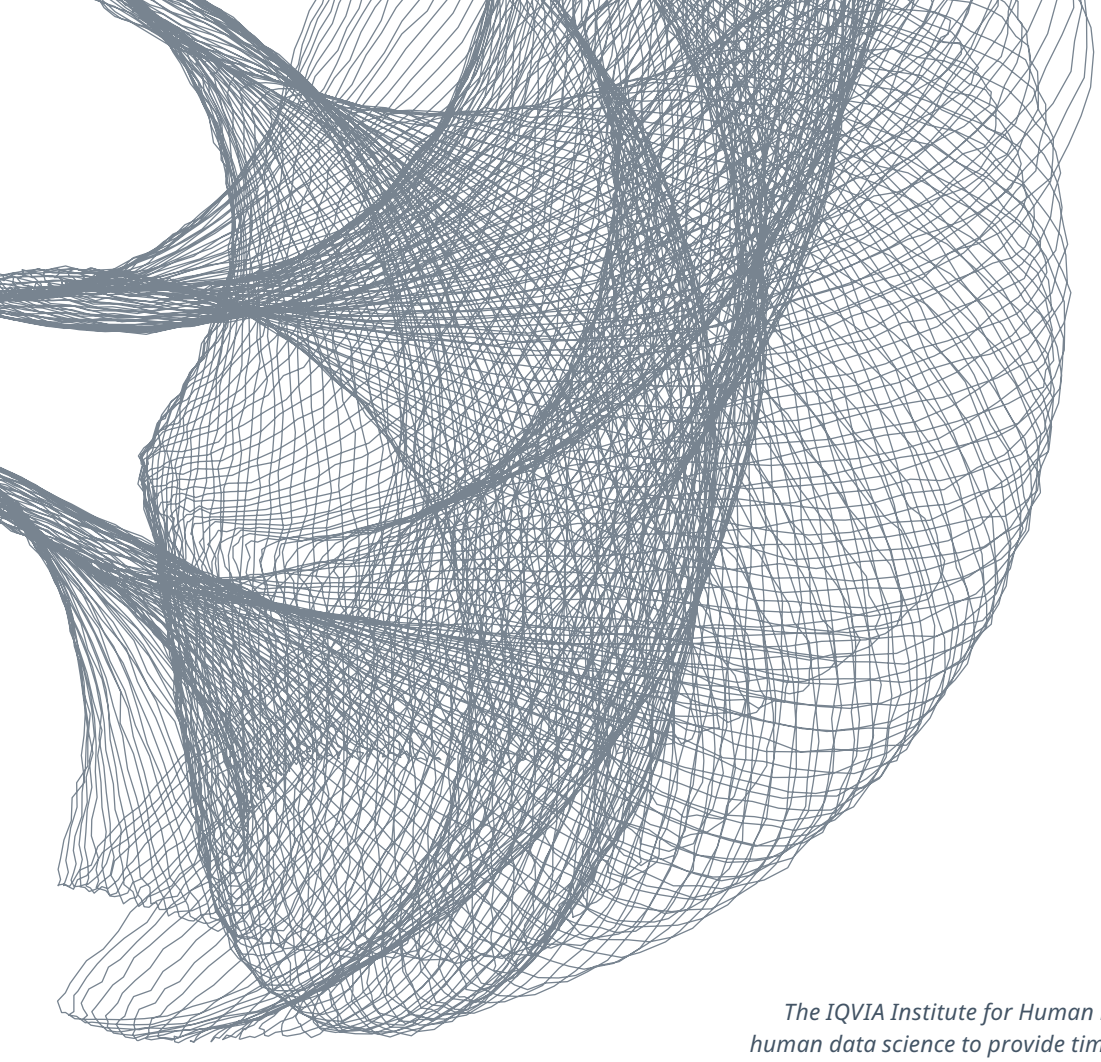
The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

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

Guiding Principles

The Institute operates from a set of Guiding Principles:

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



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

Artwork on this report cover was generated using data sets from IQVIA Patent Intelligence™, IQVIA Pipeline Intelligence ™ and research by the IQVIA Institute for Human Data Science. The data sets show drugs launched in the U.S. 2017-2018 by the originating company and the FDA filing company as well as by the type of company based on their size (emerging biopharma, small, mid-sized, or large).

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