Innovation in the Biopharmaceutical Pipeline

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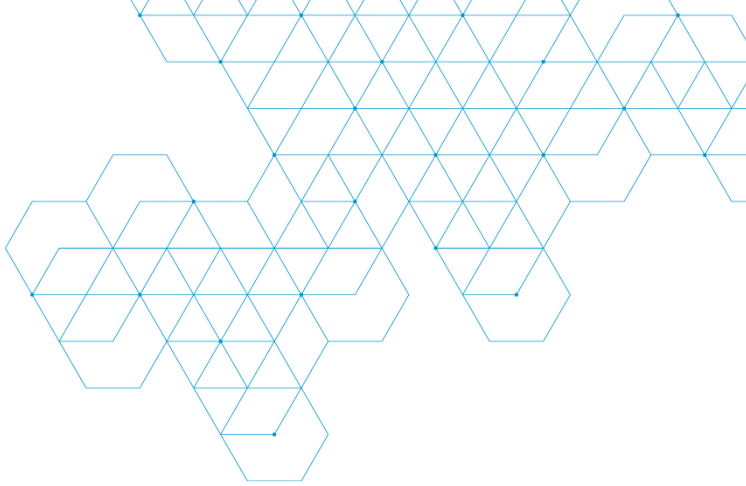


EXECUTIVE SUMMARY

Over the last two decades (between 2000 and 2020) nearly 700 new prescription medicines (new molecular entities (NMEs) and original biologic license applications (BLAs) have been approved for use by the U.S. Food and Drug Administration (FDA).[1] Together, these innovations have contributed to a range of new treatment options resulting in improvements in the length and quality of life and reduced disease burden for individuals and society. However, there remains tremendous need for innovative new therapies for some of the most challenging and costly diseases, faced by today's U.S. patients.

This study examines the state of the drug research and development (R&D) pipeline and provides insights into the development of medicines for different therapeutic areas, the distribution of clinical research projects by phase, the number of potential first-in-class medicines, and some new applications of various scientific approaches. The analysis is based on a review of data from the Evaluate Pharma database, a proprietary competitive intelligence database that curates publicly available information on companies and marketed, pipeline and discontinued products. These data are complemented by FDA data on numbers of new drug approvals and orphan drug designations. While acknowledging the global nature of drug development, this report focuses primarily on potential new medicines in clinical development and regulatory review in the U.S. as of January 2021.

Developing a new medicine is a long, expensive, and complex process, with risk of failure at each step. Some have previously estimated that only 12 percent of investigational compounds that reach clinical trials are ultimately approved by the FDA.[2] While hundreds of thousands, or even millions, of compounds may be screened as part of the search for potential drugs, and thousands of new medicine candidates are further screened for evidence of activity in the laboratory, only one may eventually result in an FDA-approved medicine, which often takes at least 10 years on average of research and development.[3]

While it is impossible to predict which of the many specific projects described in this report will eventually proceed all the way to FDA approval and ultimately benefit patients, this report provides a glimpse into the various therapeutic areas of focus and highlights some emerging areas of promise.

> Together, these innovations have contributed to a range of new treatment options resulting in improvements in the length and quality of life and reduced disease burden for individuals and society.

Key findings from the report include:

- As of January 2021, there were more than **7,800 products in clinical development globally**.
- Accounting for the fact that the same molecule may be used in clinical trials for more than one indication – with an indication referring to use for treating a particular disease or condition – these products correspond to **over 12,600 projects in clinical development** (that is, unique molecule-indication combinations; for example, a particular drug in clinical trials for use in both Alzheimer's disease and schizophrenia would be counted as two *projects, but only* one *product*).
- Development projects were distributed across **many therapeutic areas**, from cancer to cardiovascular disease and diabetes to neurology. For example, 964 projects were in clinical development in neurology alone, including 132 for Alzheimer's disease, 125 for Parkinson's disease, and 58 for ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease).
- **Nearly 70 percent** (69 percent) of clinical-phase projects were **potentially first-in-class** (i.e., described by a unique pharmacological class distinct from those of any other marketed products). While only one molecule in each class can eventually achieve first-in-class designation, it cannot be known in advance *which* molecule will proceed from clinical testing and be approved first. There were high percentages of potential first-in-class clinical-phase projects in many major therapeutic categories, including cancer (68 percent), neurology (76 percent), and cardiovascular disease (74 percent).
- Of the projects in clinical development, some **1,135 received orphan drug designation by the FDA, designated for medicines intended to treat, prevent or diagnosis a rare disease or condition**, one that affects fewer than 200,000 persons in the U.S. or meets the cost recovery provisions of the Orphan Drug Act. Qualifying for an orphan drug designation does not necessarily mean the product will ultimately be approved as an orphan drug, as the investigational medicine must still meet the criteria for FDA approval in that indication. As there are no effective treatments for most rare diseases or conditions, this portion of the pipeline represents substantial promise, with nearly 20 percent of Phase III projects and about 23 percent of projects undergoing regulatory review (i.e., having a status at the time the data were produced of being filed for approval in the U.S., or being approved but not yet launched in the U.S.) also having received orphan drug designations.

- **A range of scientific approaches** to address various diseases and conditions are being pursued in clinical development, including:
  - 1,174 projects using either **gene therapy** (281 projects), in which a patient's genes are modified to treat or prevent a disease, **cell therapy** (545 projects), in which healthy, functioning cells are introduced to treat a disease or condition in which the patient's cells are damaged or diseased, or **gene-modified cell therapy** (348 projects), in which a functional gene is introduced into a cell-based therapy (e.g., CAR-T therapies).
  - 265 projects using **DNA or RNA therapeutics** (targeting DNA and RNA, which carry and transmit genetic information that creates proteins), like antisense drugs that block messenger RNA translation and thereby prevent the production of certain disease-associated proteins.
  - 2,533 projects using **monoclonal antibodies**, or **conjugated monoclonal antibodies**, which use highly selective monoclonal antibodies joined to other agents such as chemotherapy drugs to target specific cells such as tumors, while sparing nearby healthy cells.
  - 133 projects using **oncolytic viruses**, in which tumor-seeking viruses infect tumor cells and replicate themselves until the cells burst, releasing markers that allow the cancer to be recognized by the immune system and an immune response is then mounted against the cancer.

While it is impossible to predict which of the many specific projects described in this report will eventually proceed all the way to FDA approval and ultimately benefit patients, this report provides a glimpse into the various therapeutic areas of focus and highlights some emerging areas of promise.

TABLE OF CONTENTS

Study Objectives 5

Background 6

Pipeline Metrics: Describing Innovative Therapies in Clinical Development 8

Analysis Results 10

A. Total Number of Medicines in Development, by Phase and Therapeutic Area 10

B. Potential First-in-Class Medicines in Development 14

C. Medicines in Development to Treat Rare Diseases and Conditions 18

D. Precision Medicine and Biomarkers 22

E. Scientific Approaches 23

Conclusion 25

Appendix A: The Drug Discovery and Development Process 26

Appendix B: Methodology, Definitions, and Sources 28

Appendix C: Indications by Therapeutic Area 30

STUDY OBJECTIVES

This report provides descriptive information about the current pipeline of medicines in development with the potential to address the needs of U.S. patients. It focuses primarily on medicines that have entered the clinical trial or human testing phases except where otherwise noted. The therapies in clinical testing today have the potential to result in new treatments and potential cures within the next five to 10 years, for diseases and conditions ranging from diabetes and cardiovascular disease to rare diseases for which there are currently no FDA-approved treatments.

As the COVID-19 disease pandemic hit the United States in early 2020, challenges to the pipeline of new drugs in development emerged. A myriad of challenges halted some ongoing trials and delayed new trial starts including but not limited to, trial sites could not host in-person visits; patient caseloads, even in oncology, were down sharply, delaying treatment and challenging trial enrollment; operations at clinical trial sites were severely disrupted; study staff and research resources may have been redirected to COVID-19-related projects; travel restrictions impacting travel to trial sites; and engagements with regulatory bodies were delayed.

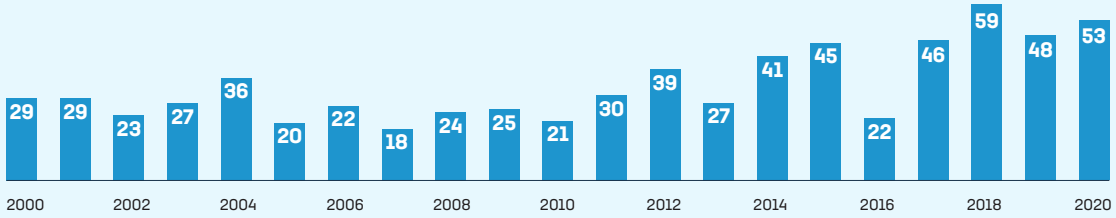
In response, innovative thinking and collaboration enabled trial continuation through such means as: transitions to remote monitoring and patient check-ins and other virtually-enabled approaches; regulatory flexibility that more readily facilitated decentralized trials so patients could receive treatments at home or other sites; master protocols to rapidly test and compare multiple investigative treatments simultaneously; harmonized data platforms and adaptive trial designs; and telehealth-based communication between patients, investigators and sites.[4] While virtually every aspect of life was disrupted around the world, the drug development community came together to drive the development, emergency authorization and approval, manufacturing and distribution of life-saving COVID therapeutics and vaccines. As of October 2021, over six billion vaccine doses have been administered worldwide.[5] Simultaneously, the biopharmaceutical industry continued to apply the same innovative changes to clinical trials to advance the pipeline of other, non-COVID-19-related and critically needed therapies. This is all happening while maintaining the manufacture and flow of already available medicines to the patients that need them.

With the pandemic ongoing, the full story of the impact on the drug development pipeline is yet to be written; rather, the statistics presented in this report provide insight into the combined efforts of patients, caregivers, researchers, government regulators, and the biopharmaceutical industry to continue the advancement of clinical knowledge and innovation during a time of unprecedented challenge.

BACKGROUND

After several years of historically low approval rates, the biopharmaceutical sector has seen an increase of new drug approval rates in recent years by the Food and Drug Administration (FDA), with some fluctuation (**Figure 1**).[6] This could be due to new insights into the genetic basis for many diseases or the accelerating application of digital technologies and artificial intelligence to the drug R&D process. To provide insight into future potential numbers of new drugs, this report provides context for understanding the drug development pipeline across thousands of diverse research projects, by quantifying and describing research activity by phase, therapeutic area, first-in-class potential, orphan drug status, and scientific platform technology.

FIGURE 1. Annual New FDA Approved Medicines Since 2000



Notes: Includes new molecular entities (NMEs) approved by the Center for Drug Evaluation and Research (CDER) under new drug applications (NDAs), and biologic license application (BLA) approvals for therapeutic biologic products. Excludes certain blood and vaccine products.

Source: US Food and Drug Administration. Figures for 2000-10 available at: https://wayback.archive-it.org/7993/20171114232132/https://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm. Figures for 2011-20 available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020. Accessed August 23, 2021. Includes figures for BLAs for 2000-03 from Mullard A. 2015 FDA drug approvals. Nature Reviews Drug Discovery 15, 73-76 (2016).

While hundreds of thousands, or even millions, of compounds may be screened as part of large-scale compound libraries, and thousands of new medicine candidates are further screened in the laboratory, only one may eventually result in an FDA-approved medicine, after many years of testing and development. AI and machine learning systems are being used more and more during the screening phase to rapidly focus in on the most promising categories of molecules. Many investigational drugs are eliminated from development prior to testing in humans through laboratory screening and preclinical testing. Others have estimated that of those compounds reaching the clinical trial phase, only 12 percent ultimately are approved by the FDA after an average of 10 to 15 years of development and over $2.6 billion in investment.[7] (For more on the drug discovery and development process see **Appendix A**.)

Even before the COVID-19 global pandemic raised a host of new challenges, R&D projects continued to confront substantial challenges. For example, one pre-covid analysis found that clinical trials are becoming increasingly complex and time consuming in terms of the number of procedures and the components of trial protocols. Since 2009 the mean number of total endpoints in a typical Phase II and Phase III protocol increased by 27 percent and the total number of procedures (including routine exams, blood work, and x-rays) increased by 44 percent. Furthermore, Phase III protocols now collect an average of 3.6 million data points per protocol, 3 times more data points than compared to ten years ago.[8]

If not addressed, these complexities may lead to continued increases in the expense and time required to successfully develop new medicines and could result in some promising potential medicines not being pursued. In response, scientists from industry, government, and academia have been working to develop new tools, methods, and pre-competitive collaborations to improve R&D efficiency. Examples of such approaches include:

- **Creating open collaborative platforms** in the early stages of drug development (through early clinical development) that help identify drug targets, as well as other models of pre-competitive consortia and collaborations that seek to strengthen the scientific understanding of disease biology.[9]
- **Enhancing IT infrastructure and using advanced data analytics tools and approaches** such as AI, for drug target identification and screening to pharmacovigilance and safety monitoring, across all therapeutic areas including oncology, central nervous system, cardiovascular, immunology and rare diseases. The rise in precision medicine and targeted therapies, as well as the demand for new treatments for rare diseases where there is no treatment available, will continue to drive the adoption of AI in drug development.[10]
- Increasing the efficiency of clinical trials through **adaptive clinical trial designs**, a design that allows for prospectively planned modification to one or more aspects of the design based on accumulating data from patients in the trial.[11] This may enable researchers to terminate studies of medicines that are unlikely to meet safety and efficacy hurdles as early as possible and optimize others. **Other approaches like master protocols**, a single overarching protocol designed to efficiently answer multiple research questions involving interventions in more than one disease, or more than one intervention in a given disease, can reduce administrative costs and increase data quality and efficiency through shared and reusable infrastructure.[12] Researchers may also find ways to enhance efficiencies in the clinical trial process by **collaborating to accelerate early phases of clinical research and utilizing allowed regulatory flexibilities** to complete some parts of the clinical trials simultaneously, without compromising patient safety or data quality.
- Elevating the patient voice in trials efficiently with new tools to measure **patient reported outcomes (PROs) and other forms of patient derived clinical data** using digital health technologies like wearables, remote monitoring, apps, text messaging and e-diaries to generate important data on the use, benefits, and risks of medicines. A pre-pandemic study identified about 540 clinical trials in the U.S. incorporating digital health tools.[13] These types of digital patient-centered tools are also enabling *decentralized clinical trial designs*. These trials are designed with fewer clinical visits at traditional trial sites, which can lead to reduced patient and caregiver burden. This also may help encourage greater participation from diverse patient populations and make accessing clinical trials easier.[14]

> One pre-covid analysis found that clinical trials are becoming increasingly complex and time consuming in terms of the number of procedures and the components of trial protocols.

PIPELINE METRICS: DESCRIBING INNOVATIVE THERAPIES IN CLINICAL DEVELOPMENT

This report presents information on potential drug projects (i.e., medicine-indication combinations) that have advanced to the clinical testing stage, except where otherwise noted, and data are grouped in various ways (e.g., by indication or therapeutic area, such as "diabetes" drugs). It is impossible to know in advance *which* specific projects will proceed to later-stage clinical trials, be submitted to regulatory bodies for approval, be launched in the U.S., and be available to patients as new treatments. Most projects, particularly in the early stages of development, will not surmount all the scientific, regulatory, and other checkpoints they face.

Given the impossibility of predicting the eventual clinical impact of today's many and varied development efforts years in the future, this report provides several different metrics describing drug development pipeline projects and new medicines in development, including:

- **Total numbers of medicines in development**, by phase and therapeutic area.
- **Potential first-in-class medicines,** those that represent a new pharmacological class or mechanism of action for treating a given disease or condition.
- **Medicines targeting rare diseases or conditions** affecting 200,000 or fewer patients in the U.S. or meeting the cost recovery requirements of the Orphan Drug Act; and
- **Total numbers of medicines in development, by scientific approach**, including those that apply scientific strategies in novel ways to address diseases that have no existing treatment option.

Each of these perspectives provides a different view of the drug development pipeline and its potential to address unmet patient needs.

Some of these measures relate to the *numbers* of potential therapies, others to the *types* of potential therapies or *patients* who may benefit from them. The analysis begins with the most straightforward descriptive measures of the drug pipeline, simple counts of new therapies in development by phase of development, and by therapeutic area.

These measures are supplemented with several others that provide information on approaches that may advance treatment, the types of diseases that would be affected should the investigational drug proceed all the way to FDA approval and launch, and indicators of the potential clinical impact for patients (i.e., whether the therapy may benefit rare disease populations with high unmet need or if the therapy has the potential to be a "first-in-class" drug in a given therapeutic area), noting that it is not possible to fully assess the medical impact of a drug while it is still in development.

Throughout the report, different scientific approaches that have the potential to target diseases in new ways (e.g., gene therapy) are highlighted. The scientific approaches reflected are not exhaustive and do not represent a value

judgment or prediction of the potential future scientific and clinical impact of these scientific approaches. Rather, as in previous versions of this report, this analysis only scratches the surface by selecting a few readily identifiable and systematically detectable approaches in the data source used for the analysis. There are surely many others that will prove to be equally (or more) important sources of innovation, but which were not readily or systematically identifiable in the data sources.

Data reflect drugs in development or under FDA review as of January 2021, unless otherwise noted.

While this report targets drugs in development for the U.S. market with the potential to aid U.S. patients, it is difficult to identify *ex ante* which drugs in development may eventually be submitted for FDA approval; research and development activity is inherently global, although regulatory review, launch, and marketing are market specific. Because most drugs are intended for marketing in the U.S., the largest market in the world, we have not excluded any drugs in clinical development (i.e., in Phases I, II, or III). However, in any counts of drugs currently in regulatory review, we have excluded drugs that were not filed with the FDA. The counts presented reflect the status of drugs in development at a given point in time (i.e., January 2021); later on, clinical development on these same drugs may have ceased, or the drugs may have proceeded to subsequent phases of development, been approved by the FDA for marketing, or been launched in one or more geographic markets.

To maintain consistency with totals reported in prior versions of this report, some vaccines in development were excluded: drugs characterized by Evaluate Pharma as having a therapeutic subcategory (as defined by ATC code) equal to "vaccine" were excluded, most of which were for infectious disease. Projects characterized as having a technology equal to "bioengineered vaccine" or "vaccine" (but with a therapeutic subcategory other than "vaccine") were retained and are included in project counts. This category includes many cancer vaccines.

A description of the methodology, definitions, and sources used is provided in **Appendix B**.

ANALYSIS RESULTS

A. Total Number of Medicines in Development, by Phase and Therapeutic Area

As illustrated in **Figure 2**, as of January 2021, there were **more than 7,800 new product** (i.e., unique molecules that would be submitted for FDA review as NMEs[15]) NDAs for NMEs or original BLAs and **more than 12,600 projects** (i.e., unique molecule-indication combinations) **in clinical development** (defined in this report as in Phase I, II, III, or having been filed with the FDA, or approved by the FDA but not yet on the market in the U.S.).[16] These figures compare to approximately 6,300 products and approximately 9,500 projects in clinical development captured using similar methods in a previous July 2017 report (reflecting data as of August 9, 2016).

Less information is publicly available about preclinical research projects and what is available publicly is likely an underestimate, so this report focuses primarily on those that have reached clinical development, except where otherwise noted.

Since a single *product* may be investigated for multiple indications, and because the data include additional indications for products already approved and on-market, the number of pipeline *projects* in clinical development is larger than the number of pipeline *products.*

Consistent with previous studies showing high attrition rates between Phase II and the much more expensive and lengthier Phase III clinical trial stage, there were fewer products counted at each progressive phase of development. Whereas there were 3,237 molecules recorded in Phase II clinical trials, there were only 1,077 products in Phase III trials. A total of 183 products in the dataset had completed Phase III clinical trials and had either been filed with the FDA or were approved by the FDA, but had not yet been launched in the U.S. Similarly, for the number of projects, there were 5,940 projects recorded in Phase II clinical trials, there were only 1,607 projects in Phase III trials, and 215 projects with drug candidates that had either been filed with the FDA or were approved by the FDA, but had not yet been launched in the U.S. Failure rates for drug candidates vary widely by phase of development and therapeutic class and can be due to a variety of reasons, such as efficacy and safety challenges, low trial enrollment or commercial viability issues.[17]

FIGURE 2. Distribution of Products and Projects by Phase

Phase	Number of Projects	Number of Products
Preclinical/ Research Project	**14,750**	**11,217**
Clinical Development	**12,689**	**7,886**
• Phase I	4,927	3,389
• Phase II	5,940	3,237
• Phase III	1,607	1,077
• U.S. Filed/Approved But Not Yet Marketed	215	183
Total	**27,439**	**19,103**

Notes: Projects and products are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects limited to those filed with the FDA. Products are unique NMEs; projects are unique product-indication combinations. Source: Author's calculations, using Evaluate Pharma data.

Figure 3 presents the number of projects in clinical development by indication or therapeutic area. While there were projects in development across the therapeutic spectrum, certain therapeutic areas, such as some cancers, infectious diseases, and neurology showed the greatest number of development projects, perhaps reflecting scientific advances in understanding the basis of these diseases and potential novel approaches and different mechanisms for disease intervention.

Oncology led the way with some 6,198 projects in clinical development, reflecting the scientific advances that have been made in understanding the causes of cancer.

Scientific Advances in the Pipeline: Cancer Immunotherapies

Biopharmaceutical innovations are leading to new strategies for delivering more personalized treatments, especially for cancer. Immunotherapy is a novel form of cancer treatment that harnesses the body's immune system to prevent, control and – in some cases – even eliminate cancer. The Cancer Research Institute describes five different approaches to cancer immunotherapy for patients across 20 cancer types, and reports that between 2017 and 2020 the immuno-oncology pipeline has grown 233%:[18]

- **Adoptive cell therapy**, also known as cellular immunotherapy, uses immune system cells to eliminate cancer either by directly isolating immune cells and increasing their numbers, or by genetically engineering immune cells to enhance their cancer-fighting capabilities (e.g., CAR-T therapy).
- **Cancer vaccines** help educate the body's immune system to recognize specific cancer cell markers, or antigens. They include preventive vaccines against cancer (such as HPV and HBV), and therapeutic vaccines that stimulate immune responses to normal, but overexpressed proteins (such as PAP and prostate cancer), or neoantigens resulting from mutations and that are specific to tumor cells.
- **Immunomodulators** target the pathways that regulate immune system activity to fight cancer, either via immune system "gas pedals" (e.g., checkpoint inhibitors) or "brakes." Other immunomodulators include cytokines, agonists, and adjuvants.
- **Oncolytic viruses** use modified viruses that can infect and destroy existing tumor cells. As of January 2021, there were 133 such projects in clinical development.
- **Targeted antibodies** disrupt cancer cell pathways and activity and alert the immune system to attack cancer cells.

After oncology, the therapeutic area with the next-highest number of projects was **neurology** with 964 projects, despite **neurological conditions** being among the most difficult to develop effective and safe new therapies due to the complexity of the scientific and clinical challenge. Of these projects, 132 were for **Alzheimer's disease**, which a recent Harris poll of retirees showed as one of the most-feared diseases, above cancer, COVID-19 disease, heart attack and stroke.[19] The development of new medicines to target neurodegenerative diseases like Alzheimer's has proven particularly challenging with a difficult record of setbacks. Between 1998 and May 2021 there were 198 unsuccessful attempts to develop medicine to treat and potentially prevent Alzheimer's.[20] Despite this challenging record of setbacks, the development pipeline reflects a continuing search for a range of effective therapies for one of the nation's most devastating and highest economic-impact diseases, including for disease-modifying therapies.

The global SARS-CoV-2 pandemic has highlighted the critical importance of investment in a continuing pipeline of **infectious disease** therapies and research into novel approaches. Results of this pipeline analysis show infectious disease as the third most common category, with 847 projects in clinical development as of January 2021. In addition to agents targeting or potentially useful for COVID-19 disease, these include projects targeting **HIV/AIDS** (82 projects in clinical

development), and **hepatitis B and C** (61 and 20 projects in clinical development, respectively; data not shown). The years of progress in basic knowledge led to the pipeline of candidates for infectious disease giving researchers critical insights into research approaches, technology platforms, and viral characteristics that helped inform the research and development of therapies and vaccines for COVID-19.

The Industry Response to COVID-19: Vaccines and Treatments

Since the beginning of the pandemic, America's biopharmaceutical companies have been developing solutions to help diagnose, treat, and prevent COVID-19, the disease caused by the novel coronavirus strain SARS-CoV-2. As of January 8, 2021, there were over 1,600 clinical trials testing more than 560 unique COVID-19 treatments, and 160 trials testing 64 COVID-19 vaccine candidates. The rapid escalation of trials for COVID-19 vaccines and treatments is a testament to a robust collaborative ecosystem and to the participation of thousands of clinical trial volunteers. [21]

Note: COVID-19 Vaccines and Treatment data analyzed with different methodology and data sources than findings in the full report.

Clinical trials in diseases like cancer, neurology, and respiratory disease were more heavily weighted toward earlier-phase trials. In cancer there were nearly six times as many Phase II trials as there were Phase III trials.

There was a higher-than-average ratio of projects per product in cancer (1.6 cancer projects per product in clinical or preclinical development, versus 1.4 overall), reflecting that different cancer indications share common pathways, so drugs may be effective across multiple indications, thus resulting in a higher number of projects per product.

Scientific Approaches in the Pipeline: DNA and RNA Therapeutics

Recent attention has focused on characterizing the underlying genetic mechanisms of disease and developing potential therapies to modify how genes function and are regulated in patients. DNA and RNA therapeutics have the potential to fix the way the gene is expressed, which can ultimately address the underlying cause of disease. There were **265 projects** in clinical research phases using DNA and RNA therapeutic approaches, including **35 projects** in Phase III or later.

DNA and RNA therapeutics include:

- **Antisense drugs** – small, chemically modified strands of DNA that block mRNA translation preventing the synthesis of unwanted proteins.
- **MicroRNA** (miRNA) and **small interfering RNA** (siRNA) drugs – small nucleic acid molecules that affect gene expression and thereby protein expression by binding to mRNA; and
- **Aptamer drugs** – nucleic acid molecules that interfere with cell signaling by binding to target molecules.

FIGURE 3. Distribution of Projects by Therapeutic Area and Phase

Therapeutic Area	Preclinical / Research Project	Number of Clinical Projects by Phase				Total Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Blood	236	80	159	73	8	320
Cancer	5,273	2,686	2,931	520	61	6,198
• Cancer, Blood & blood forming malignancies	701	681	591	86	23	1,381
• Cancer, Miscellaneous cancer	1,752	146	76	20	4	246
• Cancer, Solid tumors, Bladder	48	38	70	13	4	125
• Cancer, Solid tumors, Breast	231	137	162	36	2	337
• Cancer, Solid tumors, Colorectal	121	76	136	19	-	231
• Cancer, Solid tumors, Lung	79	14	20	2	-	36
• Cancer, Solid tumors, Melanoma	112	69	112	17	1	199
• Cancer, Solid tumors, Prostate	112	67	88	21	1	177
• Cancer, Solid tumors, Other	2,117	1,458	1,676	306	26	3,466
Cardiovascular	471	126	218	95	15	454
Diabetes	349	99	116	43	5	263
Gastro-intestinal	354	118	148	60	6	332
Hepatic & biliary	317	101	138	23	3	265
HIV & related conditions	141	33	38	9	2	82
Hormone	26	9	20	5	4	38
Immunology	851	191	196	60	16	463
Infections	1,367	263	396	167	21	847
Miscellaneous	1,152	185	153	61	20	419
Musculoskeletal	460	127	166	71	7	371
• Musculoskeletal, Rheumatoid arthritis	99	41	40	7	1	89
• Musculoskeletal, Osteoarthritis	38	16	25	10	1	52
• Musculoskeletal, Other	323	70	101	54	5	230
Neurology	1,792	397	414	143	10	964
• Neurology, ALS	90	15	25	15	3	58
• Neurology, Parkinson's disease	195	57	60	8	-	125
• Neurology, Alzheimer's disease	265	62	56	12	2	132
• Neurology, Spinal cord injury	29	7	5	3	-	15
• Neurology, Traumatic brain injury	64	6	9	1	-	16
• Neurology, Other	1,149	250	259	104	5	618
Psychiatry	178	85	110	41	2	238
Reproduction	105	23	47	18	5	93
Respiratory	474	126	183	37	3	349
Sensory organs	561	84	158	65	5	312
Skin	439	143	253	69	13	478
Surgery	46	6	12	7	1	26
Urinary Tract	158	45	84	40	8	177
TOTAL PROJECTS	**14,750**	**4,927**	**5,940**	**1,607**	**215**	**12,689**

Notes: Projects and products are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects limited to those filed with the FDA. Products are unique NMEs; projects are unique NME-indication combinations. Counts by phase may include some duplicates due to co-promotion/co-development of products. Throughout the analysis categories of "Other" and "Miscellaneous" are described in Appendix C. Source: Author's calculations, using Evaluate Pharma data.

B. Potential First-in-Class Medicines in Development

According to CDER, one "indicator of (a) drug's potential for strong positive impact on the health of the American people" is first-in-class status, which include drugs that "often have mechanisms of action, chemical structures or clinical uses, different from existing therapies."[22] First-in-class medicines provide new approaches to fight diseases, including for those with limited existing treatment options, providing important new treatment tools for physicians, and health benefits for patients.

These potentially first-in-class products may have higher development uncertainty than those having already proven mechanisms of action since there may be greater unknowns regarding the effect on both the disease and the human body. Often, multiple companies may simultaneously pursue competing approaches to similar therapeutic opportunities, and these competing compounds in development may have similar molecular structures or mechanisms of action. While only one molecule eventually can be "first-in-class" and "win the race" it may be near impossible to identify *ex ante* which will be the first to obtain FDA approval and reach patients.

It is not always the case that the molecule that entered development first will be launched first and furthermore "first-in-class" does not necessarily mean "best-in-class" in terms of efficacy and/or the safety and side effect profile for a specific patient. Often there is research and development to further differentiate subsequent medicines from the first-in-class medicine, by offering different side effects or an improved efficacy profile in different patient populations.[23] Having multiple medicines in development in the same therapeutic class is also critically important for patients, as responses to medicines can differ considerably between individuals.

This report defines potential first-in-class medicines in development as those that would be reviewed as new molecular entities (NMEs) or original BLAs, and which have a pharmacological class different from the recorded pharmacological class of any product currently marketed in the U.S.

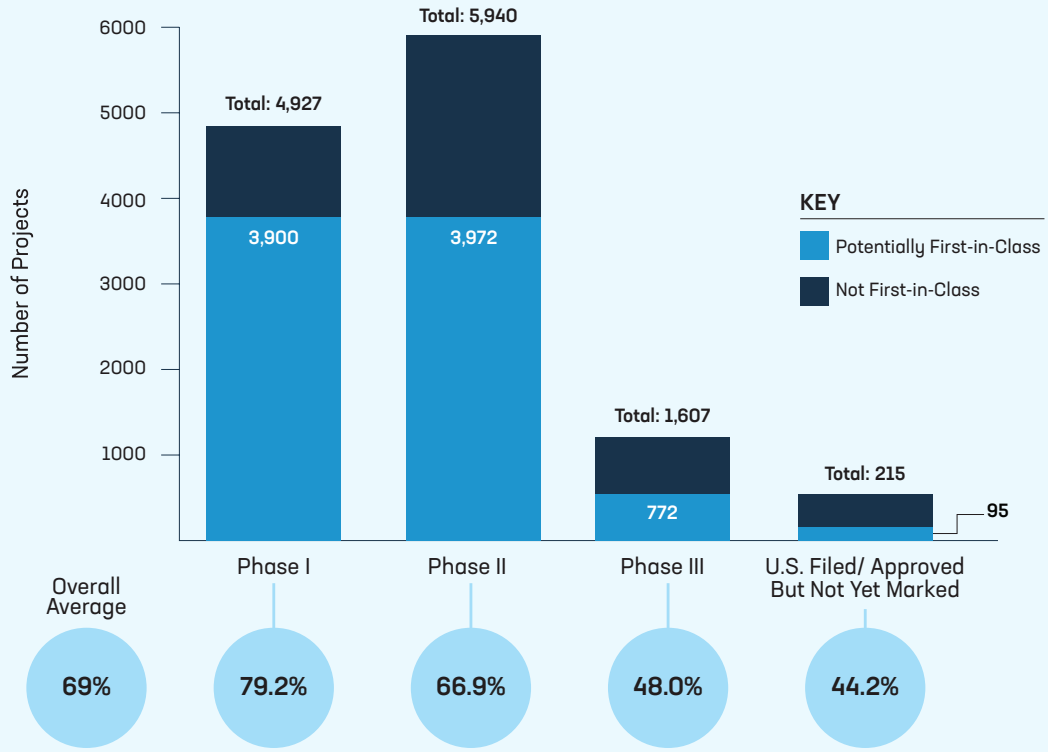
Figure 4 presents the total number of potential first-in-class medicines in development, by phase.

> First-in-class medicines provide new approaches to fight diseases, including for those with limited existing treatment options, providing important new treatment tools for physicians, and health benefits for patients.

As **Figure 4** illustrates, potential first-in-class projects represented 69 percent of the clinical pipeline overall and dominated the early phases of development – almost 80 percent of Phase I projects would be first-in-class therapies if approved now. Almost 67 percent of Phase II projects would be first-in-class, and some 48 percent of Phase III projects would be first-in-class if approved now.

The variation in first-in-class status by phase may, in part, be due to how the data for pharmacological class are recorded – as clinical development continues, the definition of a particular pharmacological class may evolve, narrow, or become more standardized, reducing the total number of different pharmacological classes with products in development for a given indication. It is also possible that there is higher attrition among potential first-in-class treatments due to greater scientific uncertainty, contributing to declining percentages over subsequent development stages. Even the figures for Phase III projects, however, would represent a high percentage of potential first-in-class therapies. In 2020, 21 of the 53 novel drugs approved (or 40 percent) were identified by CDER as being first-in-class.[24]

FIGURE 4. Potential First-in-Class Medicine Development Projects



Notes: Projects are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects are limited to those filed with the FDA. First-in-class defined as projects with a pharmacological class that is different from that of any marketed project/product (e.g., PPAR agonist, somatostatin antagonist, etc.). Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products. Source: Author's calculations, using Evaluate Pharma data.

Figure 5 presents comparable figures for potential first-in-class medicines in development, by therapeutic area. There were high percentages of potential first-in-class medicines in many therapeutic areas, including neurology (76 percent in clinical phases, including 123 potentially first-in-class projects in clinical development for Alzheimer's disease and 96 for Parkinson's disease), cancer (68 percent of projects in clinical phases, or 4,215 potentially first-in-class projects in clinical development), and cardiovascular disease (74 percent of projects in clinical phases). As scientists learn more about the underpinnings of many disease areas, new pharmacological classes and mechanisms of action are likely to emerge.

The 68 percent of potential first-in-class projects currently in the pipeline to treat different forms of **cancer** is particularly promising. Decades of research mapping the human genome and understanding the causes and progression of cancer at the molecular and cellular level are leading to more targeted treatment approaches. However, exploring new frontiers is cancer treatment is associated with high levels of scientific complexity and uncertainty and challenges in the drug development process. One analysis looking at nine different cancers found that between 1998 and 2019 a total of over 100 drugs were approved, while over 1,300 failed in the development process.[25] Despite these inherent challenges, the high level of potential first-in-class medicines reflects researchers' commitment to explore treatment approaches to a wide range of cancers – which may prove to benefit those that have seen progress in recent years, and those that have not.

For example, **ovarian cancer** remains an area with high levels of unmet need, as the disease is largely diagnosed at a late stage, at which point it is more difficult to treat. While there has been some progress in recent years in maintenance therapies that help extend the time to recurrence, continued progress is needed. Researchers continue to explore innovative approaches for these patients, reflected by the 155 potentially first-in-class projects currently in clinical development (8 of which are in Phase III).

Additionally, a high level of potential first-in-class treatments for **melanoma** reflects the continued research necessary to provide additional innovative treatment options. Melanoma is an area with remarkable progress in recent years against advanced stages of the disease, but where researchers continue to explore innovative treatment approaches, with 156 potentially first-in-class projects in clinical development.[26]

There is also a range of potentially first-in-class medicines in development in areas relevant to the needs of national security, the United States military, and victims of natural disasters. For example, research is underway to address potential bioterrorism agents that could cause death or disease in humans, and there were 556 potential first-in-class projects in clinical development for infections including 4 for **Ebola**.

Innovative research is also underway for **traumatic brain injury** and **post-traumatic stress disorder (PTSD)**, where there remains a need for therapies to treat the full spectrum of symptoms. There are 14 potentially first-in-class projects for traumatic brain injury and 6 potentially first-in-class projects in clinical development for PTSD.

FIGURE 5. Potential First-in-Class Medicine Development Projects, by Therapeutic Area

Therapeutic Area	Preclinical / Research Project	Number of Clinical Projects by Phase				Total Potential First-in-Class Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Blood	188	61	112	42	3	218
Cancer	4,701	2,173	1,812	204	26	4,215
• Cancer, Blood & blood forming malignancies	584	539	330	33	9	911
• Cancer, Miscellaneous cancer	1,625	119	33	10	4	166
• Cancer, Solid tumors, Bladder	44	33	41	3	3	80
• Cancer, Solid tumors, Breast	194	106	109	11	-	226
• Cancer, Solid tumors, Colorectal	110	54	89	10	-	153
• Cancer, Solid tumors, Lung	69	10	10	1	-	21
• Cancer, Solid tumors, Melanoma	97	64	86	6	-	156
• Cancer, Solid tumors, Prostate	100	55	60	9	1	125
• Cancer, Solid tumors, Other	1,878	1,193	1,054	121	9	2,377
Cardiovascular	433	109	175	49	3	336
Diabetes	291	71	90	25	4	190
Gastro-intestinal	244	82	113	31	1	227
Hepatic & biliary	228	64	102	14	2	182
HIV & related conditions	115	24	26	4	1	55
Hormone	20	8	10	3	2	23
Immunology	682	159	116	26	6	307
Infections	977	201	265	83	7	556
Miscellaneous	928	138	96	39	12	285
Musculoskeletal	404	103	118	29	4	254
• Musculoskeletal, Rheumatoid arthritis	83	34	27	4	-	65
• Musculoskeletal, Osteoarthritis	34	16	21	5	1	43
• Musculoskeletal, Other	287	53	70	20	3	146
Neurology	1,577	329	326	71	5	731
• Neurology, ALS	88	13	22	10	2	47
• Neurology, Parkinson's disease	177	46	47	3	-	96
• Neurology, Alzheimer's disease	249	58	53	11	1	123
• Neurology, Spinal cord injury	29	6	5	3	-	14
• Neurology, Traumatic brain injury	56	5	8	1	-	14
• Neurology, Other	978	201	191	43	2	437
Psychiatry	160	70	88	18	2	178
Reproduction	87	20	31	9	2	62
Respiratory	399	101	149	22	2	274
Sensory organs	376	51	112	39	3	205
Skin	304	97	160	40	7	304
Surgery	30	5	12	3	-	20
Urinary Tract	146	34	59	21	3	117
Total Potential First-in-Class Projects	**12,290**	**3,900**	**3,972**	**772**	**95**	**8,739**
Total Projects	**14,750**	**4,927**	**5,940**	**1,607**	**215**	**12,689**
% Potential First-in-Class	**83.3%**	**79.2%**	**66.9%**	**48.0%**	**44.2%**	**68.9%**

Notes: Projects are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects limited to those filed with the FDA. First-in-class defined as project with a pharmacological class that is different from that of any marketed project/product (e.g., PPAR agonist, somatostatin antagonist, etc.). Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products. Throughout the analysis categories of "Other" and "Miscellaneous" are described in Appendix C. Source: Author's calculations, using Evaluate Pharma data.

C. Medicines in Development to Treat Rare Diseases and Conditions

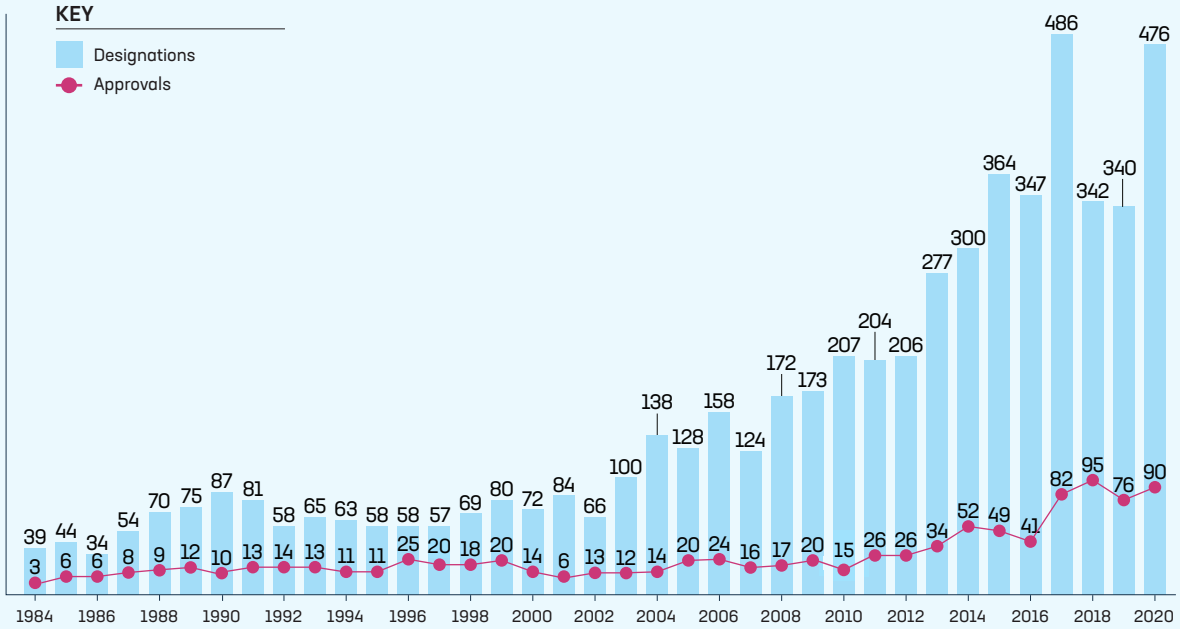
The National Institutes of Health (NIH) Office of Rare Diseases Research has identified roughly 7,000 rare diseases, which individually affect fewer than 200,000 people in the U.S. Together, rare diseases affect 25 to 30 million Americans, or roughly 1 in 10 of the U.S. population, many of them children. However, recent estimates calling for coordinated efforts to more precisely define rare diseases suggest it may be much higher.[27, 28] Among rare diseases, 85 to 90 percent are described as serious or life-threatening,[29] roughly 80 percent are thought to be genetic in origin, and over 90 percent (over 6,600 diseases) are estimated to have no approved treatment.[30] For example, pancreatic cancer, a rare cancer accounting for only 3% of all cancers in the US, with limited treatment options results in a relative five-year survival rate of only 10 percent (for 2010-2016).[31]

The development of rare disease therapies presents scientific and operational challenges that result in clinical phases taking, on average, four years longer, than for non-rare disease medicines.[32] Recognizing the high costs and risks associated with developing new medicines for scientifically complex rare diseases, and the inadequate financial incentives to develop therapies to treat small populations, Congress passed the Orphan Drug Act of 1983 to strengthen these incentives. Orphan drug designation is available to drugs and biologics intended for the treatment, diagnosis, or prevention of rare diseases or conditions. Products with orphan drug designation that are ultimately approved for the designated disease or condition receive orphan drug exclusivity – preventing FDA from approving the same drug for the same indication for seven years. The Orphan Drug Act also includes other incentives for rare disease drug development, including tax credits and grants.

The Orphan Drug Act is considered a success in encouraging the development of additional therapies for rare diseases; **Figure 6** presents FDA data on the number of products receiving FDA orphan disease designations and market approval since the passage of the Orphan Drug Act of 1983. As of August 23, 2021, the FDA reports having granted a total of 5,757 orphan designations and 943 approvals through 2020.[33] In contrast, in the 10 years before the law's passage, fewer than 10 such products were approved and marketed.

The development of rare disease therapies presents scientific and operational challenges that result in clinical phases taking, on average, four years longer, than for non-rare disease medicines.

FIGURE 6. FDA Orphan Disease Designations and Approvals



Notes: Through 2020, the FDA reports having granted a total of 5,757 orphan designations and 943 orphan designations were associated with marketing approvals. Figures may include multiple designations/approvals per molecule. Source: FDA website. Available at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm, Accessed on August 23, 2021; Analysis Group calculations.

FDA awards orphan designations for specific indications rather than for a molecule as a whole. However, the pipeline database used does not systematically identify and assign FDA orphan designations at the individual project level (i.e., for a specific molecule-indication combination). A structured manual review of the products in clinical development with orphan designations, compared to any of its indications (whether for the indications in development, or for others), were assigned most-likely indication-orphan designation matches. Many products with granted orphan designations (but not already approved) are in active development.

Some 1,135 projects covered by an orphan designation were identified in active clinical development. This may well be an underestimate due to factors such as inconsistency in the names assigned to projects between the pipeline database and the FDA orphan drug database.

Projects in late development (Phase III or under regulatory review) show higher percentages of likely orphan designations. In the set of pipeline projects:

- **20 percent** of Phase III projects were covered by an FDA orphan designation.
- **23 percent** of projects in regulatory review (i.e., U.S. filed or approved, but not yet launched) were covered by an FDA orphan designation.

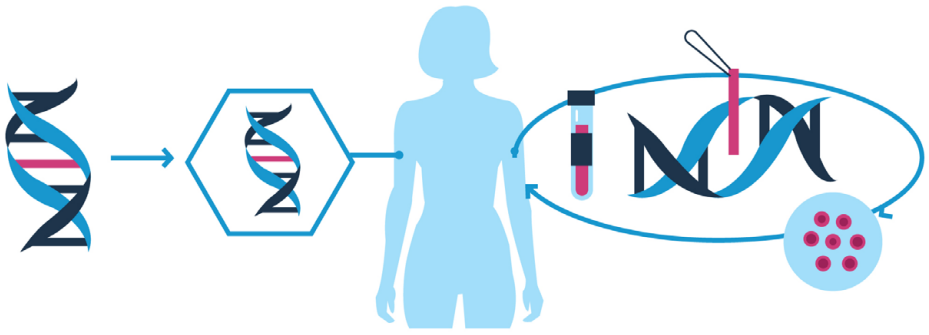
Because the total number of orphan-designated medicines in development may be under-identified in this snapshot of the drug pipeline for the reasons noted above, and because earlier-stage projects may not yet be designated as orphan products, but will be later, these counts are likely to be underestimates. The FDA reports that a high percentage of approvals, 31 of the 53 novel drugs approved by CDER in 2020, were for orphan drugs.[34]

Scientific Approaches in the Pipeline: Cell and Gene Therapy

Some 80 percent of rare diseases are estimated to be genetic in origin, providing scientists with the opportunity to address the underlying genetic mechanisms leading to many rare diseases. Regenerative medicine approaches, to regrow, repair or replace damaged or diseased cells, organs, or tissues, include cell therapy, gene therapy, and gene-modified cell therapy, as well as DNA and RNA therapeutics described above.

- **Cell therapy** is the infusion or transplantation of whole cells into a patient's body to grow, replace or repair damaged tissue to treat a disease. A variety of different types of cells may be used, including immune cells such as T-cells, and pancreatic islet cells. These strategies to replace damaged tissue can potentially treat disorders ranging from macular degeneration to ischemic heart disease. There are **545 cell therapy projects** in clinical development.
- **Gene therapy** uses DNA or RNA to manipulate a patient's cells for the treatment, prevention, or potential cure of disease. Gene therapy may include replacing a mutated gene that causes disease with a healthy copy or introducing a new or modified gene into the body. There are **281 gene therapy projects** in clinical development, including potential therapies for orphan diseases such as sickle cell anemia, Leber's congenital amaurosis (an eye disorder that can result in severe visual impairment beginning in infancy), and beta-thalassemia major (an inherited blood disorder that, if untreated, can result in severe anemia, poor growth, skeletal abnormalities during infancy, and premature death).
- **Gene-modified cell therapy** is the intersection of gene therapy and cell therapy where in some cases (e.g., CAR T-cell therapy) the cells are genetically modified before being reinfused into the patient. There are **348 gene modified cell therapy projects**, such as CAR T-cell therapy or Natural Killer (NK) T cells, in clinical development.

How Gene Therapy Works



In Vivo Gene Therapy

Sometimes a gene therapy is administered directly into the patient, where inside the body a vector brings the corrected, silenced, or replacement DNA to the cells.

Ex Vivo Gene Therapy and CAR T-Cell Therapy

Sometimes cells are taken from the patient, modified outside of the body, multiplied in a lab, and then returned to the patient.

Source: PhRMA. "Biopharmaceuticals in Perspective," Fall 2020.

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Figure 7 summarizes the distribution of these orphan-designated projects by therapeutic area. Just over half of orphan-designated projects in clinical development are in various cancers or neurology (54%), with the remainder in other indications.

FIGURE 7. Orphan-Designated Pipeline Projects, by Therapeutic Area and Clinical Development Phase

Therapeutic Area	Preclinical / Research Project	Number of Clinical Projects by Phase				Total Potential Orphan Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Blood	4	15	34	25	3	77
Cancer	99	109	266	129	16	520
• Cancer, Blood & blood forming malignancies	34	45	109	40	10	240
• Cancer, Miscellaneous cancer	2	2	3	1	-	6
• Cancer, Solid tumors, Bladder	1	-	1	-	-	1
• Cancer, Solid tumors, Breast	-	-	-	-	-	-
• Cancer, Solid tumors, Colorectal	1	-	3	-	-	3
• Cancer, Solid tumors, Lung	-	-	-	-	-	-
• Cancer, Solid tumors, Melanoma	5	4	13	8	-	25
• Cancer, Solid tumors, Prostate	-	-	-	-	-	-
• Cancer, Solid tumors, Other	56	58	137	80	6	281
Cardiovascular	8	4	12	9	2	27
Diabetes	1	1	4	1	2	8
Gastro-intestinal	6	4	6	18	2	30
Hepatic & biliary	4	3	14	6	2	25
HIV & related conditions	-	-	-	-	-	-
Hormone	2	1	7	2	1	11
Immunology	17	12	27	23	5	67
Infections	10	5	15	15	5	40
Miscellaneous	27	13	40	20	5	78
Musculoskeletal	11	7	20	11	2	40
• Musculoskeletal, Rheumatoid arthritis	-	-	-	-	-	-
• Musculoskeletal, Osteoarthritis	-	-	-	-	-	-
• Musculoskeletal, Other	11	7	20	11	2	40
Neurology	21	24	42	23	2	91
• Neurology, ALS	4	2	10	7	1	20
• Neurology, Parkinson's disease	-	-	1	-	-	1
• Neurology, Alzheimer's disease	-	-	-	-	-	-
• Neurology, Spinal cord injury	-	-	3	-	-	3
• Neurology, Traumatic brain injury	-	-	-	-	-	-
• Neurology, Other	17	22	28	16	1	67
Psychiatry	1	-	1	-	-	1
Reproduction	1	1	-	-	-	1

Respiratory	11	12	20	5	-	37
Sensory organs	13	5	18	8	1	32
Skin	5	5	12	7	1	25
Surgery	-	-	-	-	-	-
Urinary Tract	2	1	10	13	1	25
Total Potential Orphan Projects	**243**	**222**	**548**	**315**	**50**	**1,135**
Total Projects	**14,750**	**4,927**	**5,940**	**1,607**	**215**	**12,689**
% Potential Orphan Projects	**1.6%**	**4.5%**	**9.2%**	**19.6%**	**23.3%**	**8.9%**

Notes: Projects are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects limited to those filed with the FDA. Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products. Source: Author's calculations, using Evaluate Pharma data.

D. Precision Medicine and Biomarkers

Precision medicine is a treatment approach that uses diagnostic tools to identify genetic mutations, the presence of certain proteins, or other molecules that relate to a disease or its treatment, called biomarkers. Biomarkers can help determine if a patient has a disease. More technically, a biomarker is a measure or physical sign and indicator of normal processes in the body or response to an intervention, that can be used to determine how the body is functioning. This analysis found that there were over 950 projects in the pipeline that use biomarkers.

Medical professionals use biomarkers to diagnose disease, monitor how a disease is progressing and, if treatment is given, how the body is responding. Biomarkers also help determine the appropriate medicine or dose for a patient, thereby reducing uncertainty and guiding treatment. Precision medicine helps find the most appropriate treatment more quickly, prevent or reduce negative side effects, improve patients' quality of life, and treat disease more effectively.

Rapid advances in science are driving an increased understanding of human physiology and how diseases affect the body; these advances are helping researchers identify new biomarkers. This, combined with advances in genomics, have spurred better understanding of certain diseases, allowing for the development

of precision therapies based on a specific gene mutation or molecular target. The Personalized Medicine Coalition reports that there were more than 280 personalized medicines on the market in 2020, up from only 5 in 2008, with many more on the way.[35] Similarly, in 2019, 25% of New Molecular Entities (NMEs) approved by the FDA were classified as precision medicines as opposed to the 5% of NMEs classified as precision medicines in 2005.[36]

Biomarkers can improve drug development because they have the potential to serve as surrogate endpoints, markers that are expected to predict clinical benefit (but are not themselves measures of clinical benefit) and can be substituted for a clinical endpoint, thereby accelerating drug development, and

considerably shortening the time to FDA review. A 2015 survey suggested that biomarkers also continue to be important elements for drugs in development – 42 percent of the drugs in the development pipeline at that time included biomarkers in their research and development design.[37] More recently, a comprehensive study of trends over time in the use of biomarkers based on a review of all trials registered in ClinicalTrials.gov found that 55% of oncology clinical trials in 2018 involved the use of biomarkers, in comparison with just 15% in 2000.[38] Increasingly, oncology trials include biomarkers related to drug efficacy, toxicity or pharmacogenetic stratification to help identify the patients who will benefit.[39]

As of March 2021, the FDA listed 459 instances of biomarkers that provide information about a gene or protein in the labels of approved drugs, such as "germline or somatic gene variants (polymorphisms, mutations), functional deficiencies with a genetic etiology, gene expression differences, and chromosomal abnormalities; selected protein biomarkers that are used to select treatments for patients are also included."[40]

Examples of biomarkers that inform some treatments in the pipeline include the PDL1 protein which binds with a specific receptor found on T-cells, preventing tumors from blocking T-cell activation, and evading the body's immune response. Immune checkpoint inhibitor drugs for melanoma and non-small cell lung cancer, among others, target this PD1/PDL1 interaction to allow T-cells to recognize tumor cells without being deactivated by the tumor.[41] Experts hope that certain biomarkers can predict which patients could benefit most from specific treatments, increasing the share of patients who respond to treatment.

E. Scientific Approaches

Fundamental scientific research into the causes and nature of disease is a necessary precursor of new drug development, providing insights that enable new generations of therapies to

revolutionize the clinical treatment of disease. The translation of scientific discoveries into new therapies typically requires well over a decade, but these scientific "platform" innovations may be followed by several drug development projects that eventually become new treatment options for patients. For example, monoclonal antibodies (antibodies that are designed to bind to specific, targeted disease-causing entities in the body) became potential treatments for patients following a series of scientific breakthroughs in the mid-1970s and early 1980s. The FDA recently approved its 100th monoclonal antibody drug, including therapies for immunological diseases and various cancers.[42] Similarly, insights from the development of mRNA vaccines to target the SARS-CoV-2 virus may be critical to advancing entirely new approaches to cancer treatment tomorrow.

Some of the new treatment approaches being developed and tested in today's drug pipeline also may lead to future generations of new therapeutic options for patients. For example, there were over 400 cancer vaccine projects in clinical development reflected in the following table. However, the new specific technologies that are most likely to hold promise is unknown, given the uncertainties inherent in the drug development process.

Figure 8 summarizes the distribution of projects by scientific approach.

FIGURE 8. Distribution of Projects by Scientific Approach and Phase

Technology	Project	Number of Clinical Projects by Phase				Total Clinical Phase Projects
		Phase I	Phase II	Phase III	U.S. Filed / Approved	
Bioengineered vaccine	409	187	251	22	-	460
Cell therapy	840	216	286	41	2	545
Chiral chemistry	9	10	12	8	1	31
DNA & RNA therapeutics	501	109	121	31	4	265
Gene therapy	697	72	179	27	3	281
Gene-modified cell therapy	326	221	103	12	12	348
Genome editing	52	4	3	-	-	7
In vivo diagnostics	82	44	44	13	5	106
Miscellaneous	85	16	22	7	2	47
Monoclonal antibody	1,852	819	983	339	42	2,183
Monoclonal antibody (conjugated)	367	141	176	26	7	350
Oncolytic virus	101	57	70	6	-	133
Other biotechnology product	337	67	79	13	-	159
Plant extract	102	16	39	16	3	74
Plasma-derived therapy	36	8	20	17	1	46
Protein extract	228	27	50	19	3	99
Recombiant product	609	195	295	102	20	612
Small molecule chemistry	8,116	2,718	3,207	908	110	6,943
Transgenic product	1	-	-	-	-	-
Total Projects	**14,750**	**4,927**	**5,940**	**1,607**	**215**	**12,689**

Notes: Projects and products are limited to NMEs, as defined by Evaluate Pharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date but not yet be launched in the U.S. Filed projects are limited to those filed with the FDA in the U.S. For consistency with previous versions of this report, a number of vaccines in development, primarily for infectious disease, are excluded from the counts shown throughout this report. Drugs characterized by Evaluate Pharma as having a therapeutic subcategory of "vaccine" were excluded; others were retained and appear in project counts. ("Bioengineered vaccines" are those where biotechnology techniques modify the components of conventional vaccines or synthetically engineer new vaccine components; "Miscellaneous" includes a limited number of products for which technology is characterized as "vaccine"). The vaccines and bioengineered vaccines shown in this table are primarily cancer vaccines. Source: Author's calculations, using Evaluate Pharma data.

CONCLUSION

The COVID-19 pandemic has been a sobering reminder of the devastating impact of disease on patients, their families and communities, and economies around the world. At the same time, the rapid, flexible, and collaborative response of thousands of dedicated scientists, innovative companies, health professionals and regulators, illustrates the tremendous impact of innovative biomedical R&D, from enabling the continuation of clinical trials with new digital technologies and regulatory flexibilities, to the historically rapid development and deployment of life-saving vaccines.

While it is impossible to predict which of the specific projects and products in development today will eventually proceed all the way to patients, today's pipeline of potential new medicines reflects robust, diverse clinical research programs across many different therapeutic areas. The pipeline addresses both common conditions and rare diseases. Candidate medicines take varied scientific approaches, from targeting proteins in the body in new ways and harnessing the body's immune system to attack tumors, to replacing mutated, disease-causing genes with healthy copies through gene therapy. The high proportion of projects that have the potential to be first-in-class reflects exciting scientific opportunities and innovative approaches being used by researchers to address critical unmet patient needs.

The medicines in development have the potential to benefit thousands of different patient populations and subpopulations. In addition, emerging clinical results from highly precise gene editing and immunotherapy approaches for certain cancers are laying the groundwork for tomorrow's patients who currently do not have many therapeutic options.

Given the changing demographic and clinical needs of the U.S. population and the growing socioeconomic burden of disease, there is immense need for continued development of new treatments. This report provides a snapshot of the number and range of potential new treatments and cures in the drug development pipeline, representing sources of hope for current and future patients.

APPENDIX A: THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

Developing a new medicine is a long and complex process, with risk of failure at each step. Recent estimates are that the average cost to yield a single FDA-approved drug is approximately $2.6 billion.[43] The entire research and development and FDA approval process time, including compound synthesis, clinical development, and regulatory review, is 10 years or more, varying by therapeutic area.

Discovery and preclinical testing

Prior to testing in humans, a new drug candidate is considered a preclinical or discovery (rather than development) project. The focus of preclinical testing is to determine whether the drug is safe enough to use in human volunteers and whether it exhibits sufficient pharmacological activity to merit further investigation. If the candidate medicine meets these criteria, the company files an Investigational New Drug (IND) application with the FDA to permit testing in humans. The IND includes data from preclinical testing and previous experience with the drug in humans (e.g., from foreign use), manufacturing information, and detailed protocols for proposed clinical studies.

Clinical testing in human clinical trial volunteers

Drug development is staged in three successive phases.

A **Phase I clinical trial** is typically conducted in a small number of healthy volunteers, typically fewer than 100, to determine the safety, tolerability, and pharmacokinetics and pharmacodynamics of the drug (how the drug behaves in the body and the relationship between the drug's chemical structure and its effects on patients).

If a drug successfully passes Phase I testing, then **Phase II clinical trials** are conducted in patient volunteers to assess the efficacy and dose response of the drug. Phase II trials typically may enroll 100 to 500 patients and identify common, short-term drug treatment side effects.

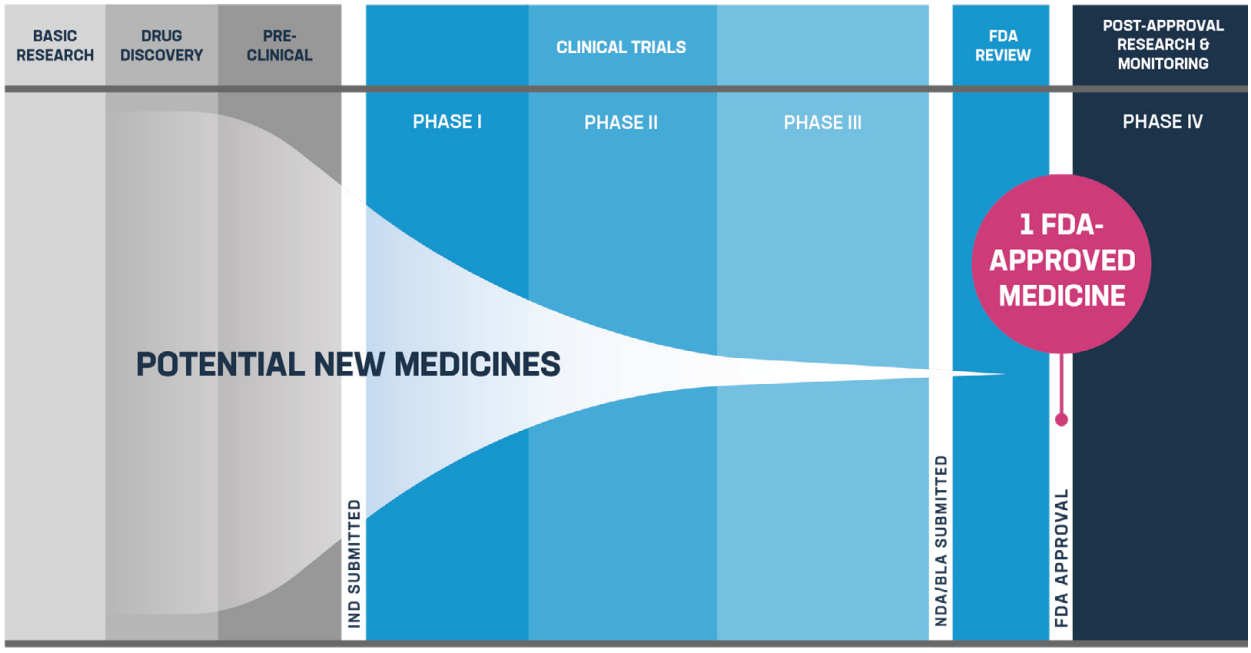
Drugs that appear as both safe and efficacious in Phase I and II clinical testing are then tested in larger randomized, controlled **Phase III clinical trials**, which might enroll at least 1,000 to 5,000 patients across numerous clinical trial sites around the world. From enrollment to completion, Phase III trials may take years to complete and cost many millions of dollars. Regulatory authorities in the U.S. and other countries typically require positive data from two Phase III trials to support a submission for market approval.

Regulatory review and approval

If the trials are successful, the data collected from preclinical studies and the full set of clinical trials are submitted to the FDA for review in the form of a New Drug Application (NDA) or Biologic License Application (BLA) (in the U.S.). If the drug is approved, the manufacturer may market it for the approved indication(s).

Post-approval research and monitoring

Phase IV clinical trials are often conducted to test the long-term safety and efficacy characteristics of approved drugs and may be required by the FDA as a condition of approval. (This report does not reflect data on post-approval research and thus does not include a review of Phase IV trials.)



Key: IND=Investigational new drug application, NDA=New drug application, BLA=Biologics license application

*The average R&D cost required to bring a new FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

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APPENDIX B: METHODOLOGY, DEFINITIONS, AND SOURCES

Except where otherwise noted, data were obtained from Evaluate Pharma, a proprietary commercial database with coverage of thousands of companies and over 100,000 marketed, pipeline or discontinued products (including those on-market, discontinued, transferred, and in development). Pipeline information is available for each stage of development, defined as: Research Project, Preclinical, Phase I, II, III, Filed, and Approved. Evaluate Pharma collects and curates information from publicly available sources and contains drug-related information (i.e. company sponsor, therapy area). The data were as of January 2021.

While this report focuses on drugs in development that have the potential to become new treatment options for U.S. patients, it is difficult to identify ex ante which drugs in development may eventually be submitted for FDA approval. Despite development activity being inherently global, regulatory review, launch, and marketing are market specific. Because most drugs are intended for marketing in the U.S., the largest drug market in the world, no drugs in clinical development (i.e., in Phases I, II, or III) were excluded. However, in any counts of drugs currently in regulatory review, drugs that were not filed with the FDA were excluded.

To maintain consistency with totals reported in prior versions of this report, some vaccines in development were excluded: drugs characterized by Evaluate Pharma as having a therapeutic subcategory (as defined by ATC code) equal to "vaccine" were excluded, most of which were for infectious disease. Projects characterized as having a technology equal to "bioengineered vaccine" or "vaccine" (but with a therapeutic subcategory other than "vaccine") were retained and are included in project counts. According to Evaluate Pharma, bioengineered vaccines are those where biotechnology techniques modify the components of conventional vaccines (e.g., attenuated viruses) or synthetically engineer new vaccine components. This category includes many cancer vaccines.

Unless otherwise noted, this analysis is restricted to new drug applications for medicines that would be reviewed **as new molecular entities (NMEs)** and to new indications for already-approved NMEs. NMEs are those active ingredients that have not previously been approved in any form. NMEs are defined by Evaluate Pharma as New Drug Application (NDA) for FDA review that contain active moieties not previously approved by the FDA either alone or in combination, or those biologics approved pursuant to a Biologics License Application (BLA) under section 351(a) of the Public Health Service Act. This definition corresponds closely to the NME definition used by FDA.

Products are defined as having a unique generic name, such that a single product is counted exactly once (regardless of the number of indications being pursued).

Projects are unique product-indication combinations, where a single product is counted for each indication in development (e.g., a molecule in development with three indications, is three projects).

Development Phase is defined as the most advanced worldwide indication status (U.S.-specific indication status is not an available field) and is defined as: Marketed, Approved, Filed, Phase III, Phase II, Phase I, and Preclinical and Research Project. Marketed projects (excluded from the reported totals) were defined as having a reported FDA approval date and a known or populated U.S. launch date; filed projects are limited to those filed with the FDA but not yet approved or marketed in the U.S.; approved projects are limited to those having a reported FDA approval date, but not yet marketed in the U.S. Analysis excludes abandoned, discontinued, withdrawn, or transferred products (i.e., those no longer being actively developed). Analysis excludes candidates with the therapeutic subcategory (as defined by ATC code) vaccine.

Other data sources used include the FDA Orphan Drug Product designation database, accessed on August 23, 2021.

APPENDIX C: INDICATIONS BY THERAPEUTIC AREA

Therapeutic Area	Indication
Blood	Bleeding disorders
Blood	Blood cell disorders
Blood	Thrombo-embolic disorders
Cancer, Blood & blood forming malignancies	Blood & blood forming malignancies
Cancer, Miscellaneous cancer	Miscellaneous cancer
Cancer, Solid tumors, Other	Solid tumors, Other
Cancer, Bladder cancer	Bladder cancer
Cancer, Breast cancer	Breast cancer
Cancer, Colorectal cancer	Colorectal cancer
Cancer, Lung cancer	Lung cancer
Cancer, Melanoma	Melanoma
Cancer, Prostate cancer	Prostate cancer
Cardiovascular	Cardiac arrhythmias
Cardiovascular	Generalized CVS disorders
Cardiovascular	Ischemic Heart Disease
Cardiovascular	Peripheral vascular disorders
Cardiovascular	Stroke
Diabetes	Diabetes complications
Diabetes	Diabetes treatment
Gastrointestinal	Acid disorders
Gastrointestinal	Inflammatory bowel disease (IBD)
Gastrointestinal	Miscellaneous gastro-intestinal disorders
Gastrointestinal	Motility disorders
Gastrointestinal	Other inflammatory gastro-intestinal disorders
Hepatic & biliary	Biliary disorders
Hepatic & biliary	Hepatic disorders
HIV & related conditions	HIV associated disorders
HIV & related conditions	HIV infections
HIV & related conditions	Malignancies
HIV & related conditions	Opportunistic infections
Hormone	Growth disorders
Hormone	Miscellaneous hormone disorders
Hormone	Pituitary disorders

Immunology	Autoimmune disorders
Immunology	Miscellaneous immunology
Immunology	Transplantation
Infections	Bacterial infections
Infections	Fungal infections
Infections	Genito-urinary infections
Infections	Parasitic infections
Infections	Respiratory infections
Infections	Viral infections
Miscellaneous	Diagnostic imaging
Miscellaneous	Lysosomal storage disorders
Miscellaneous	Metabolic disorders
Miscellaneous	Nutritional
Miscellaneous	Poisoning
Miscellaneous	Undisclosed
Musculoskeletal	Arthritis
Musculoskeletal	Arthritis related disorders
Musculoskeletal	Bone disorders
Musculoskeletal	Miscellaneous musculoskeletal
Neurology	Degenerative disorders
Neurology	Dementia
Neurology	Emesis
Neurology	Headache
Neurology	Miscellaneous neurological
Neurology	Neuropathy
Neurology	Pain
Neurology	Seizures/Convulsions
Neurology	Sleep disorders
Psychiatry	Addictions
Psychiatry	Anxiety
Psychiatry	Eating disorders
Psychiatry	Learning disorders
Psychiatry	Mood disorders
Psychiatry	Psychotic disorders
Reproduction	Female conditions

Reproduction	Male conditions
Reproduction	Miscellaneous reproduction
Respiratory	Allergy
Respiratory	Chronic obstructive airways disease
Respiratory	Miscellaneous respiratory disorders
Sensory Organs	Ear disorders
Sensory Organs	Eye disorders
Skin	Dermatoses
Skin	Infections & infestations
Skin	Miscellaneous skin disorders
Skin	Skin ulcers
Surgery	Anesthesia
Surgery	Surgical procedures
Urinary tract	Bladder disorders
Urinary tract	Kidney diseases

As defined by Evaluate Pharma.

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15. Products are characterized as: New molecular entities (NMEs); new derivatives; new drug applications (i.e., products that contains an active moiety that has been previously approved); generic drugs; biosimilars; or other (e.g., OTC products).

16. This report distinguishes between products and projects, reporting data for both where appropriate. The term "product" is used to denote a unique molecule or NME in development (e.g., a particular recombinant protein). The term "project" is used to refer to unique product and indication combinations (e.g., a particular recombinant protein for colorectal cancer, rather than breast cancer). In the counts presented for projects, a single molecule being investigated in multiple indications is counted once for each indication, reflecting the fact that distinct clinical trial activity is required for each indication. When showing counts of products, a given molecule is counted only once, and only if it has not yet been approved by FDA and is not yet on-market. In the case of projects to test additional clinical indications for products already approved by FDA and on the market, therefore, each indication is counted as a separate project, and the molecule itself is not included in the product count (if it is already approved and on-market).

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