The Biopharmaceutical Pipeline:

Innovative Therapies in Clinical Development

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Innovative Therapies in Clinical Development

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Executive Summary

Since 2000, more than 475 new prescription medicines (new molecular entities and new biologic license applications) 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, the need for innovative new therapies for some of the most challenging and costly diseases and conditions continues, given population demographics and patient need.

This study examines the state of the drug pipeline and provides insights into such areas as the therapeutic areas being explored, the distribution of clinical research projects by phase, the number of potential first-in-class medicines, and some of the new areas of scientific opportunity being applied to advance treatments. The analysis is based on a review of data from the Evaluate Pharma database, one of several proprietary competitive intelligence databases which curate publicly available information on companies and marketed, pipeline or discontinued products. These data are complemented by FDA data on numbers of new drug approvals and orphan drug designations. This report focuses primarily on potential new medicines in clinical development and regulatory review as of August 2016.

Developing a new medicine is a long and complex process, with risk of failure at each step. Others have estimated that only 12 percent of investigational compounds that reach clinical trials are ultimately approved by the FDA. While hundreds of thousands, or even millions, of compounds may be screened as part of large-scale libraries, and thousands of new medicine candidates are further screened in the laboratory, only one may eventually result in an FDA-approved medicine, after some 10 to 15 years of testing.

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.

Key findings from the report include:

- As of August 2016, there were more than ***6,300 products in clinical development*** globally.
- Taking into account that there may be clinical trials underway in more than one indication for a given molecule, these products correspond to ***over 9,500 projects in clinical development*** (that is, unique molecule-indication combinations; for example, a particular drug in clinical trials for use in 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, 739 projects were in clinical

[1] Includes new molecular entities (NMEs) approved by the Center for Drug Evaluation and Research (CDER) under new drug applications (NDAs), and since 2004 biologic license application (BLA) approvals for therapeutic biologic products. Excludes certain blood and vaccine products. Figures for 2000-10 available at: http://www.fda.gov/aboutfda/whatwedo/history/productregulation/summaryofndaapprovalsreceipts1938tothepresent/default.htm. Figures for 2011-16 available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm.

development in neurology alone, including 143 in Alzheimer's disease, 67 in Parkinson's disease, and 29 in ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease).

- ***Approximately three-quarters* (74 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 a given class can eventually win 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 therapeutic categories, including cancer (79 percent), neurology (74 percent), and diabetes (69 percent).
- Of the projects in clinical development, ***822 were determined to be covered by an orphan drug designation awarded by the FDA***. These medicines treat populations of 200,000 or fewer, such as ALS (amyotrophic lateral sclerosis) and cystic fibrosis. 17 percent of Phase III projects and 22 percent of projects currently undergoing regulatory review (U.S. filed or approved, but not yet launched) were determined to be covered by orphan drug designations; others in development may be designated by the FDA in the future, or have been designated but were not identified through the systematic manual review. 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.
- A ***range of novel scientific approaches*** to address various diseases and conditions were being pursued in clinical development, including:
  - 731 projects using ***gene therapy***, in which a patient's genes are modified to treat or prevent a disease, or ***cell therapy,*** in which healthy, functioning cells are introduced to treat a disease or condition in which the patient's cells are damaged or diseased.
  - 173 projects developing ***DNA or RNA therapeutics*** (which target DNA and RNA, which carry and transmit the genetic information that creates proteins, such as antisense drugs that block messenger RNA translation, thereby preventing the synthesis of certain disease-associated proteins).
  - 188 projects using ***conjugated monoclonal antibodies***, which use monoclonal antibodies joined to other agents such as chemotherapy drugs to target them to specific cells such as tumors, while sparing nearby healthy cells.

STUDY OBJECTIVES

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

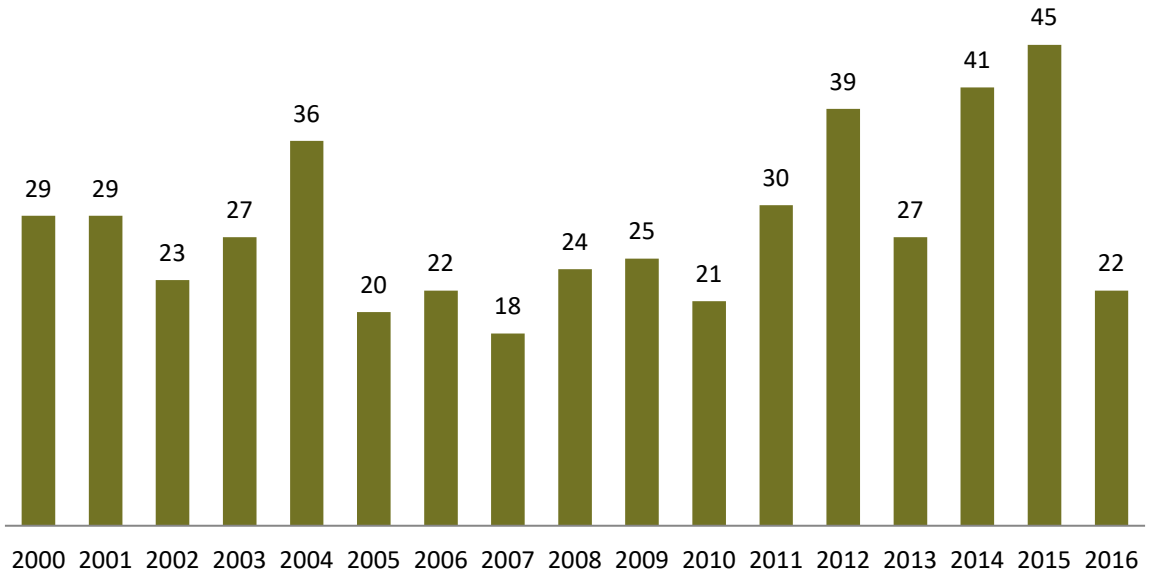
BACKGROUND

After a number of years of historically low approval rates, the biopharmaceutical sector has seen several years of higher new drug approval rates by the Food and Drug Administration (FDA), with some fluctuation (**Figure 1**).[2]

But what does the future hold? Will the advancing scientific understanding of disease mechanisms be translated into sustained levels of approved innovative treatments? By quantifying and describing research activity by phase, therapeutic area, potential to be first-in-class, orphan drug status, and scientific platform technology, this report provides context for understanding the drug development pipeline across thousands of diverse research projects.

[2] For example, in 2016, there was a reduced number of new drug approvals with a number of potential explanations cited by FDA, including some drugs expected to be approved in 2016 being approved by the end of 2015 instead; fewer new drugs being filed for approval in 2016 compared to 2015; and the FDA being able to file more complete response letters in 2016 compared to prior years, which can result in delays or withdrawal of drug applications. See, Jenkins, J. A Review of CDER's Novel Drug Approvals for 2016, FDA Voice, January 4, 2017. Available at: https://blogs.fda.gov/fdavoice/index.php/2017/01/a-review-of-cders-novel-drug-approvals-for-2016.

Figure 1. Annual New 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: http://www.fda.gov/aboutfda/whatwedo/history/productregulation/summaryofndaapprovalsreceipts1938tothepresent/default.htm. Figures for 2011-16 available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm. Accessed April 20, 2017. 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. The vast majority are eliminated 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 an average of over $2.6 billion in investment.[3] (For more on the drug discovery and development process see **Appendix A**.)

R&D projects continue to confront substantial challenges. For example, one analysis found that clinical trials are becoming increasingly complex in terms of the number of procedures and the components of trial protocols. The mean number of total endpoints in a typical Phase III protocol increased by 86 percent

[3] DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics* 2016;47:20-33.

and the total number of procedures (including routine exams, blood work, and x-rays) increased by 70 percent, comparing 2001-05 and 2011-15.[4]

If not addressed, these developments may lead to future increases in the expense and time required to successfully develop new drugs. In response, scientists from industry, government, and academia have been working to develop new tools and methods, and establish new pre-competitive collaborations in order to improve R&D efficiency. Examples of such approaches include:[5]

- *Improving validation of drug targets*, through new technologies such as "organs-on-a-chip" and through pre-competitive consortia and collaborations to strengthen scientific understanding of disease biology.
- *Enhancing IT infrastructure and data analytics* to integrate and analyze "big data" across multiple sources to more efficiently translate bench and real-world insights into trial design and clinical benefit.
- *Increasing the efficiency of clinical trials* through new approaches such as adaptive clinical trial design, in which protocols and sample sizes are modified when trials are underway, guided by interim data results, terminating studies of agents unlikely to meet safety and efficacy hurdles as early as possible, and optimizing others.

PIPELINE METRICS: DESCRIBING THE PIPELINE OF INNOVATIVE THERAPIES IN CLINICAL DEVELOPMENT

This report presents information on compounds that have advanced to the clinical testing stage, except where otherwise noted. Data are grouped in various ways (e.g., by indication or therapeutic area, such as all diabetes drugs), but it is impossible to know in advance which specific development projects will ultimately proceed to complete development, 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 and other hurdles placed before them.

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

[4] Getz KA, Campo RA. New benchmarks characterizing growth in protocol design complexity. *Therapeutic Innovation & Regul Sci.* 2017, in press; additional data on endpoints provided through correspondence with the author.

[5] See, Tufts Center for the Study of Drug Development. Profiles of new approaches to improving the efficiency and performance of pharmaceutical drug development. http://csdd.tufts.edu/files/uploads/CSSD_PhRMAWhitePaper_FINAL.pdf. Accessed November 1, 2016.

- ***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 attacking a given disease or condition;
- ***Medicines targeting "orphan" diseases*** affecting 200,000 or fewer patients in the U.S.; and
- Medicines that ***apply selected new scientific strategies to address disease*** and that may hold promise in enabling other future therapies previously impossible with existing technologies.

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, and the types of diseases that would be affected should the investigational drug proceed all the way to FDA approval and launch and the potential clinical impact for patients (i.e., whether the therapy may benefit rare disease populations that often have few therapeutic alternatives available, or whether 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 clinical impact of a drug while it is still in development.

This report also presents data on new scientific approaches that might open up alternative ways to target particular diseases (e.g., gene therapy). 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 identified novel scientific approaches, as opposed to others. Thousands of drug candidates are in development, and an individual review of each would have been impossible. Rather, this analysis only scratches the surface by selecting a few more readily identifiable, novel approaches that are systematically identifiable 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.

Results are generally for drugs in development or under FDA review as of August 9, 2016, 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 drug 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.

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 August 9, 2016, there were more than 6,300 new products (i.e., unique molecules that would be submitted for FDA review as NMEs) and 9,500 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.) in development.[6]

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*.

These figures compare to approximately 5,400 products and approximately 8,000 projects in clinical development captured using similar methods in a previous January 2013 report (reflecting data as of December 2011).

> ***Preclinical Research***
>
> Less information is publicly available about ***preclinical research*** projects, so the data in this area are less reliable – and likely an underestimate. Even so, the database used identified over 11,000 products and 15,000 projects in preclinical development.

Consistent with previous studies showing high attrition rates between Phase II and the much more expensive and lengthy Phase III clinical trial stage, there were many fewer compounds at each progressive phase of development. Whereas there were 2,660 molecules recorded in Phase II clinical trials, there were only 932 products in Phase III trials. A total of 111 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.

[6] 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 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).

New Treatment Paradigms – Personalized Medicine Progress

For the third year in a row, more than 20 percent of NMEs approved by FDA were classified as personalized medicines based on individual label review by the Personalized Medicine Coalition (6 of 22 NMEs approved by FDA in 2016).[7] The pipeline suggests a continued trend towards personalized medicine approvals. In a previous study of medicines in development, biopharmaceutical firms reported that 42 percent had the potential to be personalized medicines, increasing to 73 percent of cancer medicines.[8] In addition, the same study reported that firms estimated a 69 percent increase in the number of personalized therapies to be developed by 2020.

Scientific Advances in the Pipeline – Immunotherapies

Immunotherapy harnesses patients' immune systems to attack their cancers and holds the potential to make new inroads in the treatment of some cancers, with remission or even the possibility of cure for some. CAR T-cell therapy involves removing immune-boosting T-cells from a patient, genetically engineering them with special chimeric antigen receptors (CARs) that allow the T-cells to recognize specific tumor cell proteins so they are able to recognize and kill cancer cells, and returning the cells to the patient.[9] In recognition of its potential to improve the outlook for patients with cancer, the American Society of Clinical Oncology (ASCO) named "immunotherapy 2.0" its "2017 Advance of the Year."[10] Approximately 50 CAR T-cell therapy pipeline projects in clinical testing were identified.[11]

[7] Personalized Medicine Coalition, "Personalized medicine at FDA: 2016 Progress Report." Available at: http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM-at-FDA.pdf. Accessed April 20, 2017. The six are: rucaparib for advanced ovarian cancer; eteplirsen for Duchenne muscular dystrophy; sofosbuvir and velpatasvir combination for chronic hepatitis C infection; atezolizumab for advanced or metastatic urothelial cancer and metastatic non-small cell lung cancer; venetoclax for chronic lymphocytic leukemia; and elbasvir and grazoprevir combination for chronic hepatitis C infection. In each, decision to treat is informed by a specific biologic marker.

[8] Tufts Center for the Study of Drug Development, "Impact Report," Volume 17, No.3, May/June 2015.

[9] https://newsroom.clevelandclinic.org/2016/10/26/cleveland-clinic-unveils-top-10-medical-innovations-likley-game-changers/

[10] ASCO, "2017 Clinical Cancer Advances." Available at: http://www.asco.org/research-progress/reports-studies/clinical-cancer-advances. Accessed March 30, 2017.

[11] As of April 2017. May include duplicates and omissions.

Figure 2. Distribution of Products and Projects by Phase

Phase	Number of Projects	Number of Products
Preclinical/Research Project	**14,863**	**11,012**
Clinical Development	**9,526**	**6,321**
Phase I	*3,723*	*2,618*
Phase II	*4,424*	*2,660*
Phase III	*1,257*	*932*
U.S. Filed/Approved But Not Yet Marketed	*122*	*111*
Total	**24,389**	**17,333**

Notes: Projects and products are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. Filed projects limited to those filed with the FDA. Products are unique NMEs; projects are unique NME-indication combinations.

Source: Author's calculations, using EvaluatePharma 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 various cancers, infectious diseases, and neurology showed the greatest number of development projects, perhaps reflecting scientific advances in our understanding of the basis of these diseases and potential novel approaches and different mechanisms for disease intervention.

Oncology led the way with more than 4,000 projects in clinical development, reflecting the scientific advances that have been made in understanding the causes of cancer. This was following by ***cardiovascular disease*** with 455 projects.

Although ***neurological conditions*** historically have been among the most difficult for which to develop effective and safe new therapies due to the complexity of the scientific and clinical challenge, neurology was the third most common category of drugs in preclinical development, and the third most common in Phase III clinical trials.

Despite a challenging record of setbacks in ***Alzheimer's disease***, the development pipeline reflects a continuing search for effective therapies.[12] There is still a substantial unmet medical need, including for disease-modifying therapy. Existing drugs offer some benefits to some patients, but they treat the symptoms only. 2016 and 2017 saw high-profile failures of Phase III trials for potential therapies intended to slow the progression of the neurodegenerative disease. Despite disappointing setbacks, the pipeline reflects continued research into treatments for Alzheimer's disease, one of the country's most-feared and highest economic impact diseases.

[12] Based on a review of 413 clinical trials registered with clinicaltrials.gov between 2002 and 2012, a total of 244 drugs for Alzheimer's disease were tested and the success rate for advancing agents for regulatory approval was 0.4 percent (99.6 percent attrition) -- only one of the 244 successfully completed clinical trials and was subsequently approval by the FDA. Roughly half (53 percent) of trials conducted tested disease-modifying agents. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimer Res Therapy* 2014;6:37.

High numbers of drugs were also in development for infectious disease – including those targeting ***HIV/AIDS*** (82 projects in clinical development), and ***hepatitis B and C*** (39 and 70 projects in clinical development, respectively; data not shown).

Clinical trials in diseases like cancer, neurology, and respiratory disease were more heavily weighted toward earlier-phase trials – there were almost six times as many Phase II trials as Phase III trials under way in cancer, for instance.

There was a higher than average ratio of projects per product in ***cancer*** (1.8 cancer projects per product in clinical development, versus 1.5 overall in clinical development). Likewise, ***immunology*** had a higher than average ratio of development projects to products, reflecting that these conditions share common pathways, so drugs may be effective across multiple indications, thus resulting in a higher number of projects in development per product.

Figure 3. Distribution of Products and Projects by Therapeutic Area and Phase

Therapeutic Area	Preclinical/ Research Project	Phase I	Phase II	Phase III	Filed/ Approved	Total Projects	Total Products
Blood	293	78	104	59	3	**537**	**394**
Cancer	4,621	1,757	1,920	329	24	**8,651**	**5,789**
Cancer, Blood & blood forming malignanci	487	433	434	67	5	**1,426**	**671**
Cancer, miscellaneous cancer	1,826	100	85	21	2	**2,034**	**1,679**
Cancer, Solid tumors, Bladder	29	13	28	11	2	**83**	**27**
Cancer, Solid tumors, Breast	212	80	108	27	-	**427**	**169**
Cancer, Solid tumors, Colorectal	98	46	73	19	1	**237**	**81**
Cancer, Solid tumors, Lung	73	13	21	1	-	**108**	**50**
Cancer, Solid tumors, Melanoma	102	57	87	9	-	**255**	**154**
Cancer, Solid tumors, Prostate	146	39	86	10	-	**281**	**217**
Cancer, Solid tumors, Other	1,648	976	998	164	14	**3,800**	**2,741**
Cardiovascular	642	141	227	77	10	**1,097**	**771**
Diabetes	482	97	125	42	3	**749**	**432**
Gastro-intestinal	305	85	140	54	5	**589**	**413**
Hepatic & biliary	165	47	75	10	1	**298**	**182**
HIV & related conditions	186	30	39	13	-	**268**	**218**
Hormone	40	14	18	11	3	**86**	**62**
Immunology	1,157	200	176	60	8	**1,601**	**1,153**
Infections	1,603	195	252	109	8	**2,167**	**1,659**
Miscellaneous	916	174	116	58	6	**1,270**	**1,152**
Musculoskeletal	582	142	163	63	13	**963**	606
Musculoskeletal, Rheumatoid arthritis	165	55	52	13	2	**287**	**125**
Musculoskeletal, Osteoarthritis	62	17	31	12	1	**123**	**90**
Musculoskeletal, Other	355	70	80	38	10	**553**	**391**
Neurology	1778	320	287	119	13	**2,517**	1,899
Neurology, ALS	76	7	17	4	1	**105**	**53**
Neurology, Parkinson's disease	183	37	24	4	2	**250**	**212**
Neurology, Alzheimer's disease	276	68	52	23	-	**419**	**277**
Neurology, Spinal cord injury	45	7	9	2	-	**63**	**43**
Neurology, Traumatic brain injury	64	3	6	1	-	**74**	**70**
Neurology, Other	1,134	198	179	85	10	**1,606**	**1,244**
Psychiatry	261	76	100	29	2	**468**	**331**
Reproduction	133	23	59	27	1	**243**	**189**
Respiratory	567	126	181	50	6	**930**	**609**
Sensory organs	486	69	152	57	4	**768**	**567**
Skin	428	103	222	59	10	**822**	**624**
Surgery	72	9	18	8	1	**108**	**100**
Urinary tract	146	37	50	23	1	**257**	**183**
Total Projects	**14,863**	**3,723**	**4,424**	**1,257**	**122**	**24,389**	
Total Products	**11,012**	**2,618**	**2,660**	**932**	**111**		**17,333**

Notes: Projects and products are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. 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.

Source: Author's calculations, using EvaluatePharma data.

B. Potential First-in-Class Medicines in Development

Historically, many therapies characterized as clinical "breakthroughs" have been those that were the first to market in their therapeutic class (with a therapeutic class consisting of a group of drugs that are similar in chemical structure, pharmacological effect, mechanism of action, and/or clinical use). Because first-in-class medicines use new approaches to fight diseases, they may offer important new tools to physicians to address the unmet medical needs of patients.

These pipeline products may have higher development uncertainty than those having already proven mechanisms of action, since there may be greater unknowns regarding their effect on both disease and the human body. Frequently, multiple companies may be simultaneously pursuing 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 difficult or impossible to identify *ex ante* which will be the first to obtain FDA approval and reach patients.

In many cases, it is not the molecule that entered development first that will be launched first; in others, subsequent medicines may be further differentiated by offering different side-effect or efficacy profiles in different patient populations.[13] For example, atorvastatin was launched roughly a decade after the first marketed statin, lovastatin. With a stronger relative efficacy profile compared to the other four statins then on the market, it ultimately had higher rates of uptake among patients than the other statins.

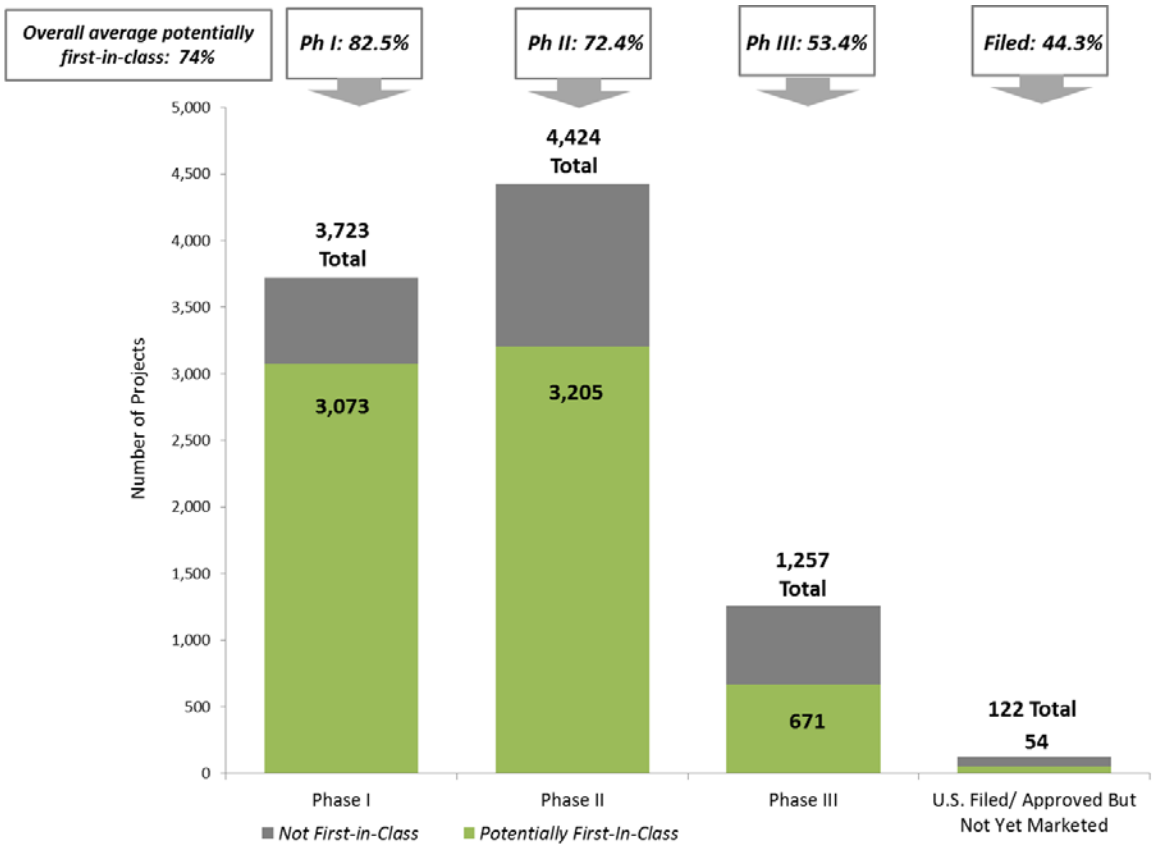
New pharmacological classes and mechanisms of action provide additional options for physicians and other health care providers to treat patients (although "first-in-class" does not necessarily mean "best-in-class" in terms of efficacy and/or the safety and side effect profile for a specific patient). First-in-class medicines may be particularly important for patients who have not responded to existing therapies, cannot tolerate the side effects associated with existing therapies, or have developed resistance to current medicines.

This report defines potential first-in-class medicines in development as those that would be reviewed as new molecular entities (NMEs), 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.

[13] J. DiMasi and C. Paquette, "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and the Timing of Development," *Pharmacoeconomics* 22 (Suppl. 2), 1–14 (2004).

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



Notes: Projects are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. 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 EvaluatePharma data.

Potential first-in-class projects represented 74 percent of the clinical pipeline overall and dominated the early phases of development –approximately 82 percent of Phase I projects would be first-in-class therapies if approved now. As **Figure 4** illustrates, roughly 72 percent of Phase II projects would be first-in-class, and some 53 percent of Phase III projects would be first-in-class if approved now.

Some variation by phase may be due to how the data for pharmacological class are recorded – the data source lists roughly 4,000 unique populated pharmacological classes in all (for any status), and as clinical testing proceeds, the definition of a particular pharmacological class is likely to evolve and may narrow and/or become more standardized. It is also possible that higher attrition among potential first-in-class treatments may contribute 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.

Figure 5 presents comparable figures for the data, presented by therapeutic area. There were high percentages of potential first-in-class medicines in many therapeutic areas, including neurology (85 percent overall and 74 percent in clinical phases, including 123 potentially first-in-class projects in clinical development for Alzheimer's disease and 53 for Parkinson's disease), cancer (85 percent overall and 79 percent of over 4,000 projects in clinical phases), and cardiovascular disease (84 percent overall and 73 percent in clinical phases). As scientists learn more about the fundamental underpinnings of many disease areas, new possible mechanisms of action are likely to emerge.

In ***cancer,*** many tumor types have proved resistant to existing drug therapies, but an improved understanding of the molecular underpinnings of these diseases is being translated into potential new medicines. For ***ovarian cancer***, there were 128 potentially first-in-class projects in clinical development (and 8 in Phase III). Given that ovarian cancer generally has a poor prognosis, there remains a need for new treatments, particularly for drug-resistant tumors. Similarly, for ***uterine cancer*** and ***lung cancer***, there were 19 and 30 potentially first-in-class projects in clinical development, respectively.

There are 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 various potential bioterrorism agents, which may cause death or disease in humans, animals, or plants, and there were 5 potentially first-in-class projects in clinical development for ***Ebola*** (if vaccines are included -- which are elsewhere excluded from the totals in this report -- the total increases to 15 potentially first-in-class clinical development projects).

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 were 10 potentially first-in-class projects for traumatic brain injury and 5 potentially first-in-class projects in clinical development for PTSD.

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

	Number of Potential First-in-Class Projects by Phase						
Therapeutic Area	Preclinical/ Research Project	Phase I	Phase II	Phase III	Filed/ Approved But Not Yet Marketed	Total Potential First-in-Class Projects	Total Projects
Blood	227	55	76	24	2	**384**	**537**
Cancer	4,190	1,536	1,459	193	14	**7,392**	**8,651**
Cancer, Blood & blood forming malignancie	439	380	317	42	3	**1,181**	**1,426**
Cancer, miscellaneous cancer	1,665	92	57	12	2	**1,828**	**2,034**
Cancer, Solid tumors, Bladder	24	9	18	6	2	**59**	**83**
Cancer, Solid tumors, Breast	177	70	83	13	-	**343**	**427**
Cancer, Solid tumors, Colorectal	78	36	58	13	1	**186**	**237**
Cancer, Solid tumors, Lung	65	13	16	1	-	**95**	**108**
Cancer, Solid tumors, Melanoma	96	53	78	9	-	**236**	**255**
Cancer, Solid tumors, Prostate	124	36	69	8	-	**237**	**281**
Cancer, Solid tumors, Other	1,522	847	763	89	6	**3,227**	**3,800**
Cardiovascular	593	117	180	31	4	**925**	**1,097**
Diabetes	414	77	92	16	-	**599**	**749**
Gastro-intestinal	221	62	92	29	1	**405**	**589**
Hepatic & biliary	117	36	50	4	-	**207**	**298**
HIV & related conditions	144	21	21	7	-	**193**	**268**
Hormone	28	8	11	5	3	**55**	**86**
Immunology	910	156	118	26	3	**1,213**	**1,601**
Infections	1,170	150	150	37	2	**1,509**	**2,167**
Miscellaneous	724	124	67	38	2	**955**	**1,270**
Musculoskeletal	520	125	130	34	6	**815**	**963**
Musculoskeletal, Rheumatoid arthritis	134	47	39	7	1	**228**	**287**
Musculoskeletal, Osteoarthritis	53	14	24	9	-	**100**	**123**
Musculoskeletal, Other	333	64	67	18	5	**487**	**553**
Neurology	1596	256	214	75	5	**2,146**	**2,517**
Neurology, ALS	73	6	12	4	1	**96**	**105**
Neurology, Parkinson's disease	161	31	18	3	1	**214**	**250**
Neurology, Alzheimer's disease	258	57	46	20	-	**381**	**419**
Neurology, Spinal cord injury	45	5	9	2	-	**61**	**63**
Neurology, Traumatic brain injury	56	3	6	1	-	**66**	**74**
Neurology, Other	1,003	154	123	45	3	**1,328**	**1,606**
Psychiatry	224	66	70	18	1	**379**	**468**
Reproduction	111	19	33	13	1	**177**	**243**
Respiratory	443	100	132	18	2	**695**	**930**
Sensory organs	452	54	122	48	1	**677**	**768**
Skin	301	73	135	38	5	**552**	**822**
Surgery	60	6	14	4	1	**85**	**108**
Urinary tract	136	32	39	13	1	**221**	**257**
Total Potential First-in-Class Projects	**12,581**	**3,073**	**3,205**	**671**	**54**	19,584	
Total Projects	**14,863**	**3,723**	**4,424**	**1,257**	**122**		**24,389**
% Potentially FIC	**84.6%**	**82.5%**	**72.4%**	**53.4%**	**44.3%**	**80.3%**	
Clinical phases only (excludes pre-clinical)							**73.5%**

Notes: Projects are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. 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.

Source: Author's calculations, using EvaluatePharma data.

C. Medicines in Development to Treat Orphan Diseases

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., but taken together affect an estimated 30 million people across the country. Among rare diseases, some 85 to 90 percent are described by the Office of Orphan Products Development as serious or life-threatening,[14] and 95 percent are estimated to have no approved treatment.[15] For example, pancreatic cancer, which affected approximately 50,000 people in the U.S. in 2013, has a relative five-year survival rate of only 7.7 percent.[16]

Recognizing that the high costs and risks associated with developing new drugs would provide 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 granted to drugs and biologics intended for the safe and effective treatment, diagnosis, or prevention of rare diseases or disorders and provides for exclusive marketing rights for the approved indication for seven years, tax credits, grants, and access to special FDA technical advice.

The Orphan Drug Act has widely been considered a success in encouraging the development of additional therapies for rare diseases; **Figure 6** presents FDA data on the number of products receiving orphan disease designations and market approval since the passage of the Orphan Drug Act of 1983. As of November 15, 2016, the FDA reports having granted a total of 3,913 orphan designations and 583 approvals. In contrast, in the 10 years before the law's passage, fewer than 10 such products were approved and marketed.[17]

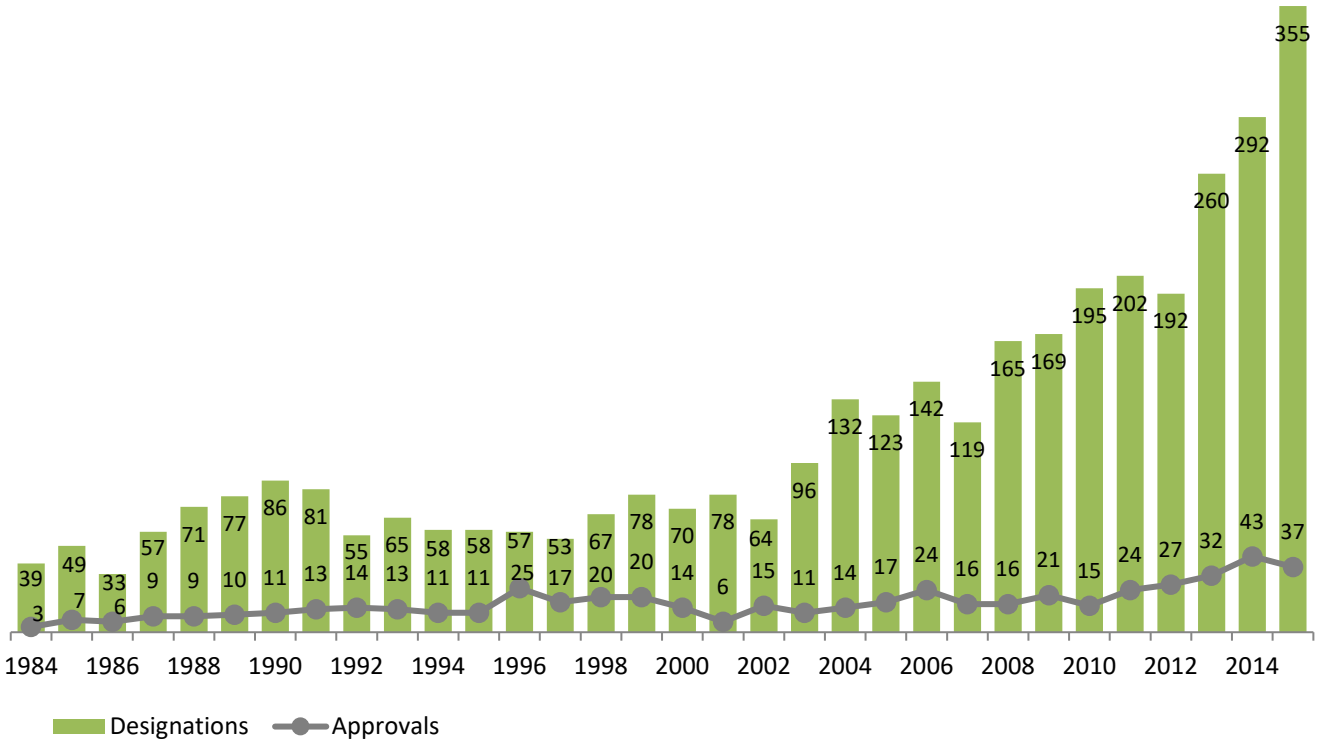
[14] U.S. Department of Health and Human Services. "Fiscal Year 2017: Food and Drug Administration Justification of Estimates for Appropriations Committee." http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM485237.pdf.

[15] Miyamoto BE and Kakkis ED. The potential investment impact of improved access to accelerated approval on the development of treatments for low prevalence rare diseases. *Orphanet J Rare Dis*. 2011 Jul 6;6:49. doi: 10.1186/1750-1172-6-49.

[16] SEER Cancer Stat Fact Sheets: Pancreas, National Cancer Institute available at http://seer.cancer.gov/statfacts/html/pancreas.html, Accessed November 1, 2016.

[17] See http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.html.

Figure 6. FDA Orphan Disease Designations and Approvals



Notes: As of November 1, 2016, the FDA reported that 3,896 orphan disease designations had been awarded, and 558 orphan designations were associated with marketing approvals.

Source: FDA website http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm, Accessed on November 1, 2016; 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). Based on a structured manual review of the products in clinical development for which orphan designations have been awarded to any of its indications (whether for the indications in development, or for others), many orphan designations awarded (but not already approved) are in active development.

Some 1,043 projects covered by an orphan designation were identified as in active development, 822 of which were in clinical development. This may 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.

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

- 17 percent of Phase III projects were covered by an FDA orphan designation;
- 22 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 for our "snapshot" of the drug pipeline for the data reporting 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 under-estimates. The FDA reports that a high percentage of approvals, or 9 of the 22 novel drugs approved in 2016, were for orphan drugs.[18]

Figure 7 summarizes the distribution of these orphan-designated projects by therapeutic area. Nearly half are in various cancers, with others in neurology and in other indications.

[18] U.S. Food and Drug Administration, 2016 Novel Drugs Summary. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf. Accessed April 20, 2017.

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

Therapeutic Area	Preclinical/ Research Project	Phase I	Phase II	Phase III	Filed/ Approved	Total Projects	Total Products
Blood	12	6	22	16	2	**58**	**43**
Cancer	70	81	217	95	8	**471**	**280**
Cancer, Blood & blood forming malignai	9	20	88	37	3	**157**	**91**
Cancer, miscellaneous cancer	2	2	3	-	-	**7**	**4**
Cancer, Solid tumors, Bladder	-	-	1	-	-	**1**	**-**
Cancer, Solid tumors, Breast	-	-	1	-	-	**1**	**-**
Cancer, Solid tumors, Colorectal	1	-	2	-	-	**3**	**1**
Cancer, Solid tumors, Lung	-	-	-	-	-	**-**	**-**
Cancer, Solid tumors, Melanoma	4	3	12	6	-	**25**	**12**
Cancer, Solid tumors, Prostate	-	-	-	-	-	**-**	**-**
Cancer, Solid tumors, Other	54	56	110	52	5	**277**	**172**
Cardiovascular	5	4	15	5	1	**30**	**25**
Diabetes	-	1	8	2	-	**11**	**10**
Gastro-intestinal	2	1	3	3	1	**10**	**8**
Hepatic & biliary	3	2	6	-	-	**11**	**6**
HIV & related conditions	-	1	1	1	-	**3**	**2**
Hormone	1	1	1	4	1	**8**	**7**
Immunology	12	10	27	20	3	**72**	**54**
Infections	18	10	12	9	1	**50**	**43**
Miscellaneous	22	11	21	19	4	**77**	**70**
Musculoskeletal	12	7	12	5	2	**38**	**27**
Musculoskeletal, Rheumatoid arthritis	1	1	-	1	-	**3**	**1**
Musculoskeletal, Osteoarthritis	-	-	-	-	-	**-**	**-**
Musculoskeletal, Other	11	6	12	4	2	**35**	**26**
Neurology	31	13	30	13	2	**89**	**67**
Neurology, ALS	10	-	6	2	-	**18**	**10**
Neurology, Parkinson's disease	-	-	1	-	-	**1**	**-**
Neurology, Alzheimer's disease	-	-	-	-	-	**-**	**-**
Neurology, Spinal cord injury	2	-	2	1	-	**5**	**5**
Neurology, Traumatic brain injury	-	-	-	-	-	**-**	**-**
Neurology, Other	19	13	21	10	2	**65**	**52**
Psychiatry	1	-	-	-	-	**1**	**1**
Reproduction	1	-	-	2	-	**3**	**3**
Respiratory	11	6	16	3	1	**37**	**29**
Sensory organs	16	4	18	7	1	**46**	**36**
Skin	3	4	5	3	-	**15**	**12**
Surgery	-	-	-	-	-	**-**	**-**
Urinary tract	1	2	8	2	-	**13**	**10**
Total Projects	**221**	**164**	**422**	**209**	**27**	**1,043**	
Total Products	**172**	**104**	**259**	**175**	**19**		**733**

Notes: Projects are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. 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 EvaluatePharma data.

D. Novel Scientific Approaches

Fundamental scientific research into the causes and nature of disease is a necessary precursor of new drug development, and insights that enable new generations of future therapies can 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 a number of drug development projects that eventually become new treatment options for patients. For example, monoclonal antibodies (antibodies that bind to specific, targeted disease-causing entities) became potential therapeutic options following a series of scientific breakthroughs in the mid-1970s and early 1980s. More than 60 monoclonal antibody drugs, primarily treating immunological diseases and various cancers, are currently marketed.

Some of the new approaches to disease being developed and tested in today's drug pipeline also may lead to future generations of new therapeutic options for patients. Which new specific technologies are most likely to hold promise is unknown, given the uncertainties inherent in the drug development process.

Figure 8 includes totals for drugs in development that rely on some of these new scientific approaches in the following categories:

- ***Cell therapy***, a type of regenerative medicine, introduces new cells into a tissue in order to treat a disease. Strategies under development include the introduction of cells that release factors with pharmaceutical benefit where the cell acts as a delivery mechanism, as well as stem cell strategies that replace damaged tissue, which have potential as eventual treatments for disorders ranging from macular degeneration to ischemic heart disease. There were 529 cell therapy projects in clinical development.

  Recent exciting therapeutic approaches in clinical development include harvesting patients' own immune cells, engineering them to recognize specific proteins on tumor cells, and re-infusing these CAR T-cells (chimeric antigen receptor T cells) back into patients to use their immune systems to attack cancer cells. Such approaches have the potential to revolutionize the treatment of some cancers, for instance for some pediatric and young adult leukemia patients, for whom the prognosis is otherwise dismal. As noted, approximately 50 CAR T-cell therapy pipeline projects in clinical testing were identified.[19]

- ***Gene therapy***, the insertion, alteration, or removal of genes within cells and tissue, is often designed to counteract original genetic defects. Products in the development pipelines employ gene therapy strategies in the hope of treating a number of genetic diseases. Recent attention has been focused on precise gene editing techniques that direct a DNA-cutting enzyme to specific genes by means of guide RNA, which has opened up new possibilities for research into how genes and gene regulators function and the effects of interventions, leading eventually to potential therapeutic interventions.

  There were 202 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

[19] As of April 2017. May include duplicates and omissions.

blood disorder that, if untreated, can result in severe anemia, poor growth, skeletal abnormalities during infancy, and can lead to premature death). Effective therapy for such diseases could result in permanent avoidance of lifelong medical interventions (such as regular blood transfusions and chelation therapy to prevent iron buildup for beta-thalassemia patients).

- ***DNA and RNA therapeutics*** include DNA, RNA or oligonucleotide analogues to treat disease, including 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 by binding to mRNA), and aptamer drugs (nucleic acid molecules that interfere with cell signaling by binding to target molecules). There were 173 projects in clinical research phases using DNA and RNA therapeutic approaches, including 23 projects in Phase III or later.
- ***Conjugated monoclonal antibodies*** are monoclonal antibodies that are joined to a cytotoxic agent that utilizes the selectivity of the antibody to deliver the cytotoxic agent to tumor cells, while sparing healthy cells. These potential medicines offer the hope of future cancer therapies that may be more effective at destroying cancer cells while reducing the side effects associated with the destruction of unintended "bystander" cells. There were 188 conjugated monoclonal antibody projects in clinical development.

As of August 2016, there were over 1,000 projects in clinical development and regulatory review using these approaches.

As noted earlier, the selected innovative scientific approaches highlighted here are those that are readily identified in the database and are provided for illustration; others less easily identified may be equally, or more promising from the point of view of patient clinical benefit, or innovative in their scientific approach.

Figure 8. Examples of Selected Scientific Strategies

	Number of Projects by Phase				
Therapeutic Area	Phase I	Phase II	Phase III	US Filed/ Approved But Not Yet Marketed	Total Projects
Cell therapy	216	276	34	3	529
Gene therapy	79	105	17	1	202
DNA & RNA therapeutics	62	88	21	2	173
Monoclonal antibody (conjugated)	106	71	11	-	188
Total Projects	463	540	83	6	1,092

Notes: Projects and products are limited to NMEs, as defined by EvaluatePharma. U.S. Filed/Approved But Not Yet Marketed phase projects must have a reported FDA approval date. Filed projects are limited to those filed with the FDA in the U.S. Novel technology is defined as the listed technologies, from the list of all technologies assigned in dataset, which include: small molecule chemistry, vaccine, chiral chemistry, **antisense therapies**, protein extract, plant extract, in vivo diagnostic, bioengineered vaccine, **cell therapy**, **gene therapy**, monoclonal antibody, **monoclonal antibody (conjugated),** recombinant product, and **transgenic products**. (Products in bold reflect those selected.) Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products.

Source: Author's calculations, using EvaluatePharma data.

CONCLUSION

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, to harnessing the body's immune system to attack tumors. 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.

Together, the medicines in development have the potential to benefit many different patient populations and subpopulations. In addition, early-stage investigation with highly precise gene editing, and emerging clinical results from new techniques such as immunotherapy approaches for certain cancers is laying the groundwork for tomorrow's breakthrough therapies for patients with few other therapeutic alternatives.

The need for continued development of new treatments is great, given the changing demographic and clinical needs of the U.S. population and the growing socioeconomic burden of disease. 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 (including out-of-pocket costs of $1.4 billion and time costs of $1.2 billion, and including the cost of development failures).[20] 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 to be 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 subjects

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 to be both safe and efficacious in Phase I and II clinical testing are next tested in larger randomized, controlled ***Phase III clinical trials***, which might enroll 1,000 to 5,000 patients (or more) 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.

[20] Calculated from a set of 106 randomly selected new drugs obtained from a confidential survey of 10 pharmaceutical firms; in 2013 dollars, when capitalized using a real discount rate of 10.5 percent, and including the cost of development failures. Sensitivity analyses provided for alternative costs of capital assumptions. DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics* 2016;47:20-33.

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.)

APPENDIX B: METHODOLOGY, DEFINITIONS, AND SOURCES

Except where otherwise noted, data were obtained from EvaluatePharma, a proprietary commercial database with coverage of over 7,000 companies and approximately 110,000 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. EvaluatePharma collects and curates information from publicly available sources and contains drug-related information such as company sponsor and therapy area. The data were downloaded on August 9, 2016.

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 – 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 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.

Unless otherwise noted, the analysis in this report 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 EvaluatePharma as candidates pursuing a New Drug Application (NDA) for FDA review that would be granted exclusivity for products containing new molecular entities never previously approved (either as the parent compound or as a salt, ester, or derivative of the parent compound) by the FDA either alone or in combination, or those biologics pursuing a Biologics License Application (BLA) under section 351(a) of the Public Health Service Act. This definition generally corresponds closely to that used by the FDA to define NMEs.

EvaluatePharma defines a ***New Drug Application (NDA)*** as a classification given to a product that contains an active molecule that has been previously approved, when the application contains reports of new clinical investigation (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to approval of the application.

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 once for each indication in development (e.g., a molecule in development with three indications would be counted as 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 reported FDA approval date and a known or populated U.S. launch date; Filed projects are limited to those filed with the FDA. Analysis excludes abandoned, discontinued, withdrawn, or transferred products (i.e., those no longer being actively developed).

Other data sources used include the FDA Orphan Drug Product designation database, accessed on November 1, 2016.

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

Therapeutic Area	Indication
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 EvaluatePharma.

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