Innovation in the Biopharmaceutical Pipeline:

A Multidimensional View

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January 2013

The authors gratefully acknowledge support from the Pharmaceutical Research and Manufacturers of America. Responsibility for the analysis presented lies entirely with the authors, who are responsible for any errors or misstatements.

Executive Summary

The U.S. innovative biopharmaceutical industry leads the world in the development of new medicines: over the past decade some 300 new prescription medicines have been approved for use by the U.S. Food and Drug Administration (FDA). Together, these innovations have contributed to a range of new treatments 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 costly and challenging diseases and conditions has never been greater.

This study presents data on two types of potential new treatments in the research and development pipeline:

- New medicines in development, or ***new molecular entities (NMEs)*** – data for which are referred to in this report as new ***"products"***; and
- ***New molecule-indication combinations*** in development (which may be NMEs or new indications for medicines previously approved by the FDA) – data for these unique molecule-indication combinations are referred to in this report as ***"projects."***

In both cases, we have focused our review on those activities that have advanced to the clinical testing stage in human volunteers, except where otherwise noted. In addition to excluding preclinical research, several other types of innovative activities were beyond the scope of this report. While new and enhanced methods of delivery and new formulations also represent new treatment options for patients and their health care providers, the study's scope was limited to new molecules and new molecule-indication combinations. Similarly, post-approval research and Phase IV trials were beyond the scope of the analysis. The study is based on a review of data from 1986 onward from EvaluatePharma, a proprietary commercial database containing information on over 4,500 companies and 50,000 products, complemented by data on clinical trials found on ClinicalTrials.gov, and on orphan drug designations in the FDA Orphan Drug Product database.

Developing a new medicine is a long and complex process, with risk of failure at each step. While thousands of new medicine candidates are screened in the laboratory, only one may eventually result in an FDA-approved medicine, after 10 to 15 years of testing, development, and review. It is impossible to predict which of the specific products or projects described in this report will eventually proceed all the way to FDA approval and ultimately to patients.

Key findings from the report include the following:

- The pipeline of drugs contained ***over 5,400 products in clinical development*** (i.e., those which have advanced to clinical testing in human volunteers, but have not yet been launched).
- Taking into account the fact that a single molecule may be undergoing or have undergone clinical trials in more than one indication, there were nearly ***8,000 projects in clinical development*** (that is, unique molecule-indication combinations; e.g., a particular drug in clinical trials for use in Alzheimer's disease and schizophrenia would be counted as one *product* and two *projects*). Development projects were distributed across many therapeutic areas, from cancer to cardiovascular disease and diabetes, to neurology. For example, more than 1,600 projects were under way in neurology alone.

- A high percentage of NME-focused development activities were ***potentially first-in-class*** (i.e., those described by a unique pharmacological class distinct from those of any other marketed products): 78 percent of projects in Phase I, 69 percent in Phase II, and 45 percent in Phase III were potentially first-in-class. Only one molecule in a given class can eventually win first-in-class designation; however, it cannot be known in advance which molecule will proceed through clinical testing and be approved first. There were particularly high percentages of potential first-in-class medicines in neurology (84 percent), psychiatry (80 percent), cancer (80 percent), and diabetes (79 percent).
- As of October 2011, 1,795 projects with an ***orphan disease*** designation by the FDA were in development. These activities address a broad range of diseases and conditions from enzyme storage disorders to rare cancers. Orphan diseases individually affect fewer than 200,000 people in the U.S., but taken together are estimated to affect some 25 million people.
- A number of potential medicines in development would provide new clinical options for patients with ***diseases for which no new therapies have been approved for many years***. An analysis of 15 selected diseases with no approvals in the past 10 years identified over 400 projects in development.
- ***Personalized medicine*** approaches are receiving a growing emphasis in development. A separate analysis of data on only Phase III and Phase IV U.S. clinical trials involving the use of molecular biomarkers (i.e., characteristics that can guide treatment and diagnosis and are integral to personalized medicine) identified 155 personalized medicine trials that were initiated on or before January 2009.
- A ***range of novel scientific approaches*** to address various diseases and conditions were being pursued. Broad classes of scientific "platforms" readily identifiable in the dataset revealed:
  - 245 projects using cell therapy;
  - 127 projects using antisense RNA interference therapy (an approach that targets RNA, which carries genetic information that creates proteins, rather than proteins themselves);
  - 102 projects using monoclonal antibodies joined to cytotoxic agents to target tumor cells while sparing nearby healthy cells; and
  - 99 projects using gene therapy.

THE CONTINUING NEED FOR NEW MEDICINES

The U.S. biopharmaceutical industry leads the world in the development of new medicines. Consistent with the Congressional Budget Office's finding that this sector is one of the nation's most research-intensive,[1] the most recent annual survey of members of the Pharmaceutical Research and Manufacturers of America reports that its members invested almost $50 billion in 2011 in discovering and developing new medicines, representing the majority of all biopharmaceutical research and development (R&D) spending in the U.S.[2]

Biopharmaceutical innovation has led to improvements in length and quality of life and reduced disease burden for individuals and society. New medicines have transformed patients' health and quality of life in many areas, from heart disease to HIV/AIDS to cancer to mental health disorders.[3] For example, since the introduction of multiple effective therapies against HIV/AIDS starting in 1995, the HIV/AIDS death rate has fallen by 83 percent in the United States.[4] Given many groundbreaking advances in the scientific understanding of the underlying mechanisms of disease, the future holds great promise for further improvements in human health and the potential to reduce the socioeconomic burden of disease.

The need for continued development of new treatments is also great, given demographic trends and public health considerations. For instance, the direct costs to all payers of caring for those with Alzheimer's disease, including out-of-pocket costs to patients and their families, is estimated to increase five-fold, from $172 billion in 2010 to $1.1 trillion in 2050, unless new treatments are found that delay its onset or slow its progression.[5]

STUDY OBJECTIVES

This report aims to provide descriptive information about the current pipeline of medicines in development with the potential to aid U.S. patients from a range of different data-driven perspectives. It focuses on medicines that have entered clinical testing in human volunteers and are therefore closer to launch than those still in preclinical development or in animal testing, except where otherwise noted.

The drugs in clinical testing with human volunteers today are the therapies that have the potential to drive new treatments and potential cures over the next five to 10 years for a range of diseases and conditions, from diabetes and cardiovascular disease to rare diseases and disorders for which an effective therapy has yet to be developed.

[1] Congressional Budget Office, "Research and Development in the Pharmaceutical Industry" (2006).

[2] Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey (Washington, D.C.: PhRMA, 2012).

[3] See, e.g., CASCADE Collaboration, "Determinants of Survival Following HIV-1 Seroconversion After Introduction of HAART," *The Lancet*, 362 (2003):1267–1274; F. R. Lichtenberg, "The Expanding Pharmaceutical Arsenal in the War on Cancer," National Bureau of Economic Research Working Paper No. 10328 (Cambridge, MA: NBER, February 2004); Tufts Center for the Study of Drug Development, "Personalized Medicine Is Playing a Growing Role in Development Pipelines," *Impact Report* 12 (Nov/Dec 2010): 6.

[4] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Health, United States (2003): With Chartbook on Trends in the Health of Americans (Hyattsville, MD: HHS, 2003); S.L. Murphy, J. Xu, and K.D. Kochanek, "Deaths: Preliminary Data for 2010," *National Vital Statistics Reports* 60, no. 4 (Hyattsville, MD: National Center for Health Statistics, January 2012): 17 (accessed 10 March 2012).

[5] Alzheimer's Association, "2012 Alzheimer's Disease Facts and Figures" (2012).

IN BRIEF: THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

Developing a new medicine is a long and complex process, with risk of failure at each step. It has been estimated that the average cost to yield a single FDA-approved drug is approximately $1.2 billion (including the cost of development failures),[6] and the entire research and development and FDA approval process time is between 10 and 15 years.[7]

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.

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.

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 U.S. Food and Drug Administration (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 indications.

[6] In 2005 dollars, when capitalized using an 11.5% discount rate, and including the cost of development failures. J.A.DiMasi and H.G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial & Decision Economics* (2007) 28:469–479.

[7] J.A. DiMasi, "New Drug Development in U.S. 1963–1999," *Clinical Pharmacology & Therapeutics* 69, no. 5 (2001): 286–296; M. Dickson and J.P. Gagnon, "Key Factors in the Rising Cost of New Drug Discovery and Development," *Nature Reviews Drug Discovery* 3 (May 2004): 417–429; J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22 (2003): 151–185.

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.)

As noted, while many thousands of compounds are screened in the lab, only one of these thousands may result eventually in an approved medicine, after many years of testing and development. The vast majority are eliminated prior to testing in human beings through laboratory screening and preclinical testing. Others have calculated that the probability of a drug that begins the next step, clinical trials in human subjects, proceeding all the way to market launch is approximately 20 percent.[8]

Because most potential medicines in development will never proceed through rigorous screening and testing procedures all the way to launch, most R&D expenditures go toward projects that do not survive the long testing, development, and approval process. As a result, R&D costs must be borne by the very few projects that proceed all the way to FDA approval and benefit patients.

Overview of R&D Challenges

Debate continues over the long-term outlook for medical innovation, with industry analysts and others expressing differing perspectives on the potential for continued innovation across the biopharmaceutical development pipeline, various indicators of R&D productivity such as the relationship between the level of R&D spending and eventual pipeline approvals, and whether the historical pace of new drug innovation can be sustained.

An increase in the level of real investment in R&D, coupled with a flat to declining number of annual new molecular entity (NME) approvals by the FDA, has led to concerns among some about the level of pipeline productivity over time (i.e., “how much” innovation is being produced per dollar spent on R&D).

Figure 1 presents figures for annual and cumulative new drug approvals by the FDA’s Center for Drug Evaluation and Research (CDER), including both NMEs and BLAs.

[8] For compounds first tested in human subjects from 1993 to 2004. J.A. DiMasi et al., “Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs,” *Clinical Pharmacology & Therapeutics*| vol. 87, no. 3 (March 2010), 272–277.

Figure 1. Annual and Cumulative New Drug Approvals Since 2000

Notes: New drug approvals include New Molecular Entities (NMEs) and biologic license applications (BLAs).
Source: Asher Mullard, "2011 FDA Drug Approvals," *Nature Reviews Drug Discovery* 11, no. 2 (February 1, 2012): 91–94.

Others have examined factors affecting the cost, duration, and uncertainties associated with clinical trials, which continue to challenge the current drug development economic model. (See "R&D Challenges: Increasing Procedure Intensity in Clinical Trials.") In response, scientists from industry, government, and academia have been working to develop new tools and methods in order to improve R&D efficiency, including such approaches as computer-based models to predict how a candidate drug is absorbed, distributed, and eliminated from the body. Better predictive models would improve the efficiency of the drug development process by either narrowing the patient population where the drug has the best chance of success, or eliminating candidate drugs before risky and costly clinical trials begin. As a result, candidate drugs in clinical trials would have a better chance of working, and fewer clinical trials might be needed to establish safety and efficacy. In addition, researchers are collaborating on pre-competitive research in areas such as biomarkers in order to accelerate research progress.

R&D Challenges: Increasing Procedure Intensity in Clinical Trials

A recent analysis found that clinical trials are becoming increasingly complex in terms of the number of procedures and total clinical staff time involved and the challenge of enrolling and retaining patient volunteers. The four-year period between 2004 and 2007 saw an increase of 49 percent in median procedures per clinical trial as compared with the previous four-year period from 2000 to 2003 and a decrease of 21 percent in patient volunteer enrollment rates (as a result of more demanding patient eligibility criteria).[1] If not offset, these developments may lead to future increases in the expense and time required to successfully develop new drugs.

[1] Tufts Center for the Study of Drug Development, "Rising Protocol Complexity, Execution Burden Varies Widely by Phase and TA," Impact Report 12, no. 3 (May/June 2010).

DESCRIBING THE PIPELINE: THE MANY DIMENSIONS OF BIOPHARMACEUTICAL INNOVATION

This report presents information on compounds that have advanced to the clinical testing stage in human volunteers, except where otherwise noted. Data on them 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 hurdles placed before them. These data have been supplemented in some cases with information from the literature to provide additional insights on selected trends and examples.

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

- ***Total numbers of medicines in development***, by therapeutic area (e.g., cardiovascular disease, diabetes, psychiatry, and neurology);
- ***Potential first-in-class medicines***, those that introduce a new mechanism of action or pharmacological class for attacking a given disease or condition;
- ***Medicines targeting rare "orphan diseases"*** affecting 200,000 or fewer patients in the U.S. (e.g., amyotrophic lateral sclerosis, or Lou Gehrig's disease);
- Medicines targeting ***diseases for which there have been no recently approved therapies***;
- Medicines that incorporate a ***"personalized medicine" approach***, tailored to specific subpopulations of patients based on molecular or genetic characteristics; and
- Medicines that are ***among the first to apply new scientific strategies to address disease*** and that may hold promise in enabling other future therapies previously impossible with existing technologies (e.g., gene therapy, therapeutic vaccines for cancer).

Each of these perspectives provides a different view of the drug development pipeline and its potential to address challenging diseases and patient needs. Some of these measures relate to the *numbers* of therapies, others to the *types* of 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 drug proceed all the way to FDA approval and launch and the potential clinical value to patients (i.e., whether the therapy may benefit "orphan 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 or provide a treatment where there have been no recent other approvals), noting that it is not possible to fully assess the clinical value of a drug so early in its life cycle (i.e., while the drug is still in development).

This report also presents data on whether drug development followed a "personalized medicine" approach and whether the therapy would be among the first to apply certain new scientific approaches that might open up new ways to target diseases (e.g., gene therapy, therapeutic vaccines for cancer). The scientific approaches reflected are not exhaustive and do not represent a value judgment or prediction of the potential future scientific and clinical value 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, we acknowledge that we have only scratched the surface in selecting a few more readily identifiable, highly novel approaches that are systematically identifiable in the data source used for the analysis. There are surely many others that are equally important (or possibly more important) sources of innovation in terms of "opening the door" to other future novel therapies for patients, but which were not readily or systematically identifiable in our data sources.

Results are generally for drugs in development or under FDA review as of December 12, 2011, unless otherwise noted.

While our interest is in 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; 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 A.

ANALYSIS RESULTS

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

As illustrated in Figure 2 below, as of December 2011, there were more than 17,000 projects (i.e., unique molecule-indication combinations) in clinical development and a total of about 12,000 products (or new medicines that would be submitted for FDA review as NMEs) in development. [9]

- ***Preclinical research*** accounted for the highest number of projects (over 9,000) and potential new medicines (over 6,500). These figures are likely an underestimate, as many preclinical research activities may not yet have been the subject of news or analyst coverage or may only be known to the researchers and manufacturers involved, and therefore would not yet be reflected in the dataset.
- Over 5,400 new products were in ***clinical development*** (defined in this report as products 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.). 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, or about 8,000.

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 2,329 molecules recorded in Phase II clinical trials, there were only 833 products in Phase III trials. A total of 82 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.

[9] As noted earlier, this report distinguishes between *products* and *projects*, reporting data for both where appropriate. We use the term "product" to denote a unique molecule or NME in development (e.g., a particular recombinant protein). We use the term "project" to refer to unique product and indication combinations (e.g., a particular recombinant protein for colorectal cancer, rather than breast cancer). In the counts we present of projects, a single molecule being investigated in multiple indications will be 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 will be 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).

Figure 2. Distribution of Products and Projects by Phase

Phase	Number of Projects	Number of Products
Preclinical/Research Project	**9,090**	**6,551**
Clinical Development	**7,982**	**5,408**
Phase I	*3,025*	*2,164*
Phase II	*3,764*	*2,329*
Phase III	*1,099*	*833*
U.S. Filed/Approved But Not Yet Marketed	*94*	*82*
Total	**17,072**	**11,959**

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: Authors' 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.

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. High numbers of drugs were also in development for cancer and infectious disease – including those targeting HIV/AIDS. Clinical trials in diseases like cancer, neurology, and respiratory disease were more heavily weighted toward earlier-phase trials – there were approximately four times as many Phase II trials as Phase III trials under way; for others such as blood diseases, infections, and reproductive conditions, there were twice as many.

There was a higher ratio of projects to products in cancer, perhaps reflecting the growing understanding of the disease at a molecular-mechanism rather than organ-system level; compounds were being investigated for multiple cancers that have similar underlying mechanisms, but which may affect different organ systems. (See "Mapping Common Cancer Pathways: Genetic Profiling of Colorectal Cancer and Other Tumors May Reveal New Cancer Treatments.") Immunology also had a higher 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	Number of Projects by Phase					Total Projects	Total Products
	Preclinical / Research Project	Phase I	Phase II	Phase III	U.S. Filed / Approved But Not Yet Marketed		
Blood	188	58	82	41	4	373	266
Cancer Total	2,400	1,265	1,507	288	13	5,473	3,436
Cancer, Blood	*239*	*243*	*277*	*55*	*4*	*818*	*383*
Cancer, Miscellaneous cancer	*922*	*126*	*59*	*14*	*2*	*1,123*	*865*
Cancer, Solid tumors, Bladder	*21*	*10*	*20*	*4*	*1*	*56*	*27*
Cancer, Solid tumors, Breast	*118*	*45*	*119*	*20*	*-*	*302*	*95*
Cancer, Solid tumors, Colorectal	*81*	*48*	*81*	*15*	*1*	*226*	*63*
Cancer, Solid tumors, Lung	*95*	*65*	*156*	*34*	*-*	*350*	*142*
Cancer, Solid tumors, Melanoma	*54*	*51*	*75*	*12*	*1*	*193*	*105*
Cancer, Solid tumors, Prostate	*119*	*53*	*92*	*18*	*1*	*283*	*217*
Cancer, Solid tumors, Other	*751*	*624*	*628*	*116*	*3*	*2,122*	*1,539*
Cardiovascular	434	128	230	85	7	884	650
Diabetes	349	103	132	43	3	630	412
Gastrointestinal	232	78	116	49	6	481	349
Hepatic & biliary	55	23	31	3	-	112	69
HIV & related conditions	141	62	48	16	2	269	204
Hormone	19	6	8	7	-	40	29
Immunology	747	126	123	45	4	1,045	731
Infections	1,295	304	289	135	22	2,045	1,586
Miscellaneous	424	107	66	50	9	656	590
Musculoskeletal	435	102	148	52	1	738	454
Neurology	1,043	256	273	74	7	1,653	1,247
Psychiatry	177	85	120	35	-	417	303
Reproduction	76	32	60	28	4	200	157
Respiratory	400	123	198	47	2	770	485
Sensory Organs	319	47	120	35	4	525	399
Skin	255	73	154	44	3	529	412
Surgery	33	13	16	9	1	72	67
Urinary tract	68	34	43	13	2	160	113
Total Projects	9,090	3,025	3,764	1,099	94	17,072	
Total Products	6,551	2,164	2,329	833	82		11,959

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: Authors' calculations, using EvaluatePharma data.

Mapping Common Cancer Pathways: Genetic Profiling of Colorectal Cancer and Other Tumors May Reveal New Cancer Treatments

Colorectal cancer is the fourth most common cancer, and some 50,000 Americans die from the disease each year. Recent research by a national consortium of 150 researchers at dozens of institutions brought together through the Cancer Genome Atlas (CGA) project provided new insights into the complex cascade of genetic abnormalities that are associated with colorectal tumors. The study systematically analyzed the genetic irregularities in over 200 tumors, identifying common pathways and their frequency. This comprehensive analysis provides insights into the biology of colorectal cancer and identifies potential therapeutic targets and approaches, such as a combination of existing drugs that targets effects related to genetic mutations that also occur in other cancers, such as melanoma. As researchers gain deeper understanding of how genetic alterations operate across many cancers through common genetic pathways, they will be better able to identify potential new drug targets.

The CGA project plans to profile genomic changes in 20 cancer types. To date, results have also been published on glioblastoma and ovarian cancer, and studies of lung cancer, breast cancer, and acute myeloid leukemia are planned next.

The Cancer Genome Atlas Network, "Comprehensive Molecular Characterization of Human Colon and Rectal Cancer," *Nature* 487, 330–337.

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). A potential "first-in-class" medicine is defined as a product with a unique pharmacological class unlike that of any marketed project/product (e.g., statins in high cholesterol, beta blockers in high blood pressure control). 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 be found to have higher clinical uncertainty than pipeline products having proven mechanisms of action, since there may be greater unknowns regarding their effect on both the 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 is 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.[10] For example, atorvastatin (Lipitor®) was launched roughly a decade after the first marketed statin, lovastatin (Mevacor®). With a

[10] 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).

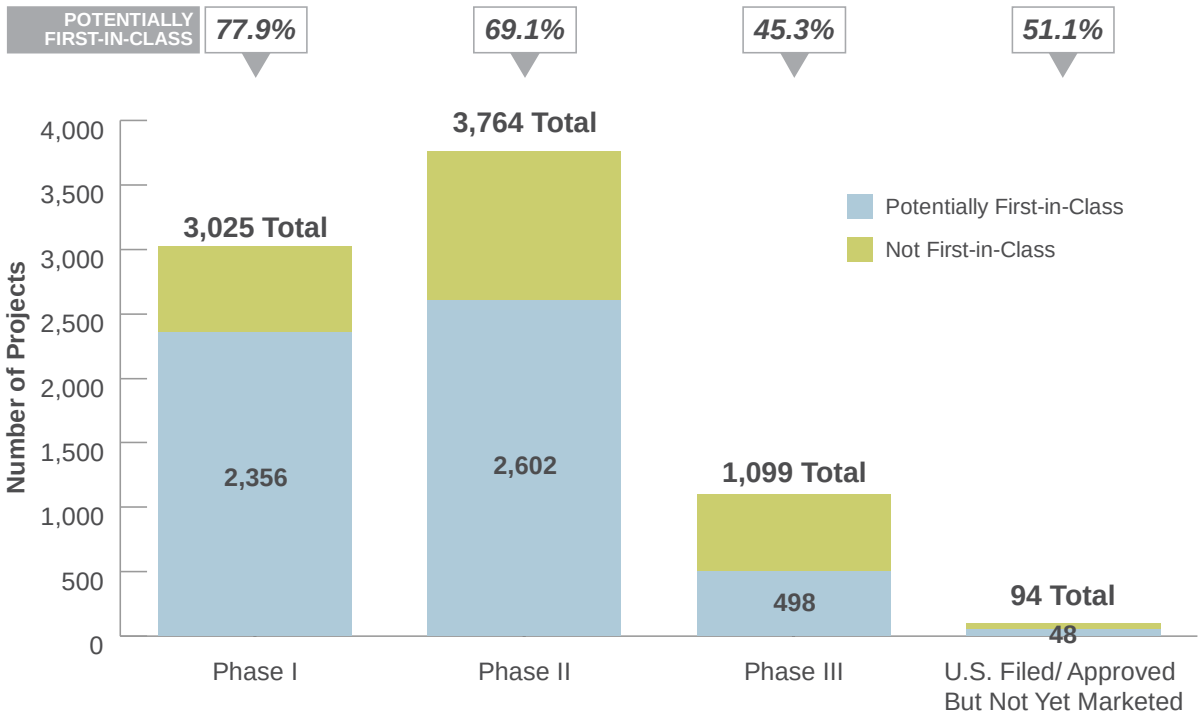
stronger relative efficacy profile compared to the other four statins then on the market, it ultimately had higher rates of uptake among patients than the other statins.

New mechanisms of action and pharmacological classes 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 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.

Potential first-in-class medicines in development were identified as those that would be reviewed as new molecular entities (NMEs), and which had 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.

Figure 4. Potential First-in-Class Medicines in Development



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 projects with a pharmacological class that is different from that of any marketed project/product (e.g., PPAR agonist, somatostatin antagonist, etc.) – EvaluatePharma lists 3,600+ unique "pharmacological classes." Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products.

Source: Authors' calculations, using EvaluatePharma data.

Potential first-in-class projects dominated the early phases of development – approximately 80 percent of Phase I projects would be first-in-class therapies if approved now. As Figure 4 illustrates, roughly 70 percent of Phase II projects would be first-in-class, and 45 percent of Phase III projects would be first-in-class if approved now. Some of this variation by phase may be due to how the data for pharmacological class are recorded – the data source lists over 3,600 unique possible pharmacological classes, and as clinical testing proceeds, the definition of a particular pharmacological class is likely to evolve and may narrow. 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 more than 20 different therapeutic areas. There were particularly high percentages of potential first-in-class medicines in neurology (84 percent, including 312 for Alzheimer's disease and 149 for Parkinson's disease), psychiatry (80 percent), cancer (80 percent), and diabetes (79 percent). As scientists learn more about the fundamental underpinnings of many disease areas, new possible mechanisms of action are likely to emerge.

Spotlight on Potential First-in-Class Drugs: Type II Diabetes and Schizophrenia

A New Approach to Controlling Type II Diabetes

Type II diabetes accounts for approximately 90 percent to 95 percent of all diagnosed cases of diabetes, which together affect 25.8 million Americans, or more than 8 percent of the U.S. population. Because Type II diabetes is the seventh leading cause of death in the United States and a major contributor to heart disease and stroke, effective control and prevention is a major public health priority. A potential new medicine in development for Type II diabetes is designed to control blood sugar levels, or glycemia, independent of insulin pathways. The medicine causes excess glucose and its associated calories to be excreted in the urine, thereby lowering blood glucose levels, weight, and blood pressure. The compound, a sodium glucose cotransporter-2 inhibitor, shows promise for patients who have trouble controlling their glucose levels with current therapies.

Addressing Difficult-to-Treat Symptoms of Schizophrenia

Schizophrenia is a chronic, severe, and disabling mental disorder affecting approximately 1 percent of the U.S. population. Current schizophrenia treatments primarily address such symptoms of the disease as hallucinations and delusions, but often do not control such symptoms as lack of motivation and interest in social activities, and becoming socially isolated. A potential first-in-class agent (a glycine reuptake inhibitor) could help normalize transmission of glutamate, a chemical that is essential in allowing brain cells to communicate with each other. This potential new medicine could be one of the first to address effectively some of these particularly challenging symptoms associated with schizophrenia.

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

Therapeutic Area	Number of Potential First-in-Class Projects by Phase					Total Potential First-in-Class Projects	Total Projects
	Preclinical / Research Project	Phase I	Phase II	Phase III	U.S. Filed / Approved But Not Yet Marketed		
Blood	137	34	52	9	2	234	373
Cancer Total	2,103	1,057	1,043	149	6	4,358	5,473
Cancer, Blood	*200*	*211*	*189*	*25*	*2*	*627*	*818*
Cancer, Miscellaneous cancer	*817*	*107*	*42*	*6*	*1*	*973*	*1,123*
Cancer, Solid tumors, Bladder	*20*	*9*	*10*	*3*	-	*42*	*56*
Cancer, Solid tumors, Breast	*103*	*37*	*83*	*7*	-	*230*	*302*
Cancer, Solid tumors, Colorectal	*71*	*41*	*58*	*11*	*1*	*182*	*226*
Cancer, Solid tumors, Lung	*83*	*54*	*109*	*18*	-	*264*	*350*
Cancer, Solid tumors, Melanoma	*51*	*49*	*65*	*10*	*1*	*176*	*193*
Cancer, Solid tumors, Prostate	*106*	*43*	*54*	*8*	-	*211*	*283*
Cancer, Solid tumors, Other	*652*	*506*	*433*	*61*	*1*	*1,653*	*2,122*
Cardiovascular	382	112	178	37	3	712	884
Diabetes	302	78	99	17	3	499	630
Gastrointestinal	168	58	85	28	3	342	481
Hepatic & biliary	43	18	21	1	-	83	112
HIV & related conditions	103	47	31	5	-	186	269
Hormone	12	2	6	2	-	22	40
Immunology	558	98	71	17	1	745	1,045
Infections	748	182	171	42	13	1,156	2,045
Miscellaneous	324	83	46	25	6	484	656
Musculoskeletal	367	80	116	26	1	590	738
Neurology	926	218	202	38	3	1,387	1,653
Psychiatry	152	66	92	21	-	331	417
Reproduction	50	18	26	12	-	106	200
Respiratory	322	86	141	28	1	578	770
Sensory organs	291	35	86	18	3	433	525
Skin	150	45	92	14	2	303	529
Surgery	28	10	13	3	1	55	72
Urinary tract	64	29	31	6	-	130	160
Total Potential First-in-Class Projects	7,230	2,356	2,602	498	48	12,734	
Total Projects	9,090	3,025	3,764	1,099	94		17,072

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.) – EvaluatePharma lists 3,600+ unique "pharmacological classes." Counts by phase may include a limited number of duplicates due to co-promotion/co-development of products. Diabetes originally classified under "hormone" class.

Source: Authors' calculations, using EvaluatePharma data.

C. Orphan Diseases

The National Institutes of Health (NIH) Office of Rare Diseases Research has identified close to 7,000 rare diseases, which individually affect fewer than 200,000 people in the U.S., but taken together affect an estimated 25 million people across the country. Most of these diseases are serious or life-threatening, and the vast majority have few or no treatment options. For example, pancreatic cancer, which affected an estimated 44,000 people in the U.S. in 2011, has a relative five-year survival rate of only 6 percent.[11]

Recognizing that the very high costs of 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 seven years, tax credits, grants, and access to special FDA technical advice.

Spotlight on Orphan Diseases: Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis: Finding Treatments for Patients with Debilitating Lung Disease

Idiopathic pulmonary fibrosis (IPF) is a debilitating and almost uniformly fatal disease in which patients experience progressive difficulty breathing due to scarring of the lungs. There are currently no effective treatment options available, and the average patient with IPF dies within three years of diagnosis. The Pulmonary Fibrosis Foundation estimates that between 120,000 and 200,000 Americans currently suffer from the disease. A medicine in development targets connective tissue growth factor, which is elevated in the lungs of IPF patients. Researchers recently announced promising results from a Phase II trial in which 60 percent of IPF patients were able to stabilize their disease or experience improvement in lung function.[1]

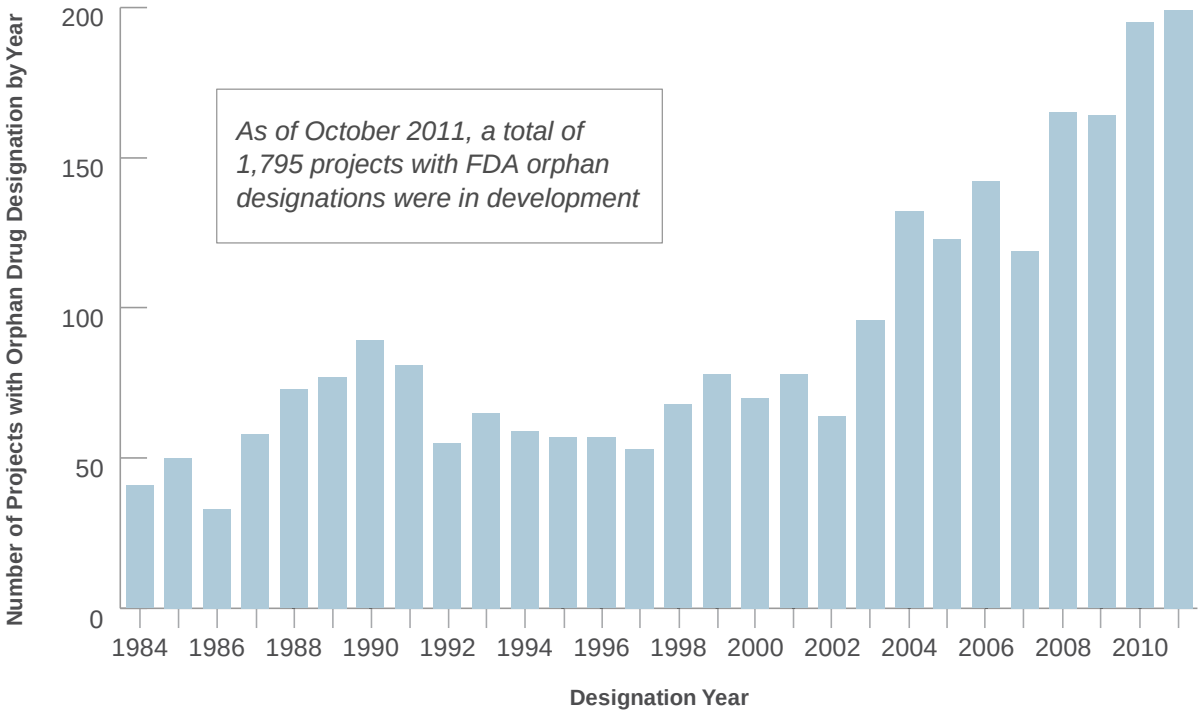
[1] Pulmonary Fibrosis Foundation, Fibrogen Announces Presentation of Updated Results at European Respiratory Society Annual Congress, http://www.pulmonaryfibrosis.org/node/839

[11] SEER Cancer Stat Fact Sheets: Pancreas, National Cancer Institute available at http://seer.cancer.gov/statfacts/html/pancreas.html, Accessed on 12/12/2011.

Figure 6 presents FDA data on the number of products receiving orphan disease designations since the passage of the Orphan Drug Act of 1983. Between 1984 and 2011, the FDA reports granting a total of 2,626 orphan designations. Excluding the 831 projects that have been either approved or withdrawn results in 1,795 orphan designations for projects in the development pipeline.[12] Between 1984 and 2011, more than 350 drugs with orphan designations were approved for marketing. In contrast, in the 10 years before the law's passage, fewer than 10 such products were approved and marketed.[13]

Orphan drug approvals accounted for 30 percent of approvals in the most recent five-year period, and the average population size for orphan designations was approximately 39,000 patients.[14]

Figure 6. Orphan Disease Designation by the FDA Over Time



Notes: As of October 2011, the FDA reported that 2,626 projects were designated for orphan disease between 1984 and 2011. Excluding 831 projects that were subsequently approved or withdrawn results in a total of 1,795 orphan designations for projects in the development pipeline at that time.

Source: FDA website http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm, Accessed on 10/20/2011; Analysis Group calculation.

[12] http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (July 20, 2012)

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

[14] M. Miles Braun, Sheiren Farag-El-Massah, Kui Xu, and Timothy R. Coté, "Emergence of Orphan Drugs in the United States: A Quantitative Assessment of the First 25 Years," *Nature Reviews Drug Discovery* 9, 519–522 (July 2010)

D. Therapies Targeting Diseases with No Recently Approved Therapies

A number of potential medicines in development would provide new clinical options for patients with diseases for which no new therapies have been approved for many years. In some cases, a lack of recent new drug approvals is a consequence of a particularly challenging, poorly understood disease. For example, the first and only therapy for ***amyotrophic lateral sclerosis (ALS)*** was approved in 1995; as of December 2011, there were over 20 new drugs in development for ALS, two of them in Phase III trials.

In other examples, strides have been made in addressing clinical treatment gaps with the approval of new medicines in disease areas with historically limited therapeutic options, and other medicines are in development to provide additional therapeutic options.

An example of a recently approved therapy (i.e., one no longer in the pipeline) addressing such a gap is belimumab (Benlysta®), the first new drug approved for ***lupus*** in the U.S. for 50 years. A number of other new drugs are in development for lupus. (See "Spotlight on Therapies Targeting Diseases with No Recently Approved Therapies: Recent Progress Against Lupus.").

For the majority of ***cystic fibrosis*** (CF) patients, no new therapies have been approved by the FDA since 1993; as of December 2011 there were over 20 drugs in clinical development for CF, with four in Phase III trials. For patients with a rare form of CF, the first medicine to address the underlying cause of the disease, ivakaftor (Kalydeco®), was recently approved. Industry collaboration with the Cystic Fibrosis Foundation led to the successful development of ivakaftor. (See "Spotlight on Recent Personalized Medicines: Melanoma, Lung Cancer, and Cystic Fibrosis.")

In the example of ***Alzheimer's disease***, although there have been three medicines approved for Alzheimer's disease since 2000, 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. Alzheimer's disease is one of the largest and fastest-growing diseases in the U.S., both in terms of human suffering and costs to the health care system. Over 5 million Americans, or one in eight people age 65 or over and almost half of individuals age 85 or over, were estimated to have Alzheimer's disease in 2012. By 2050, the number of Americans with Alzheimer's disease is expected to triple without advances that would prevent, slow, or stop disease progression. Without such improvements, direct costs are expected to increase from approximately $170 billion in 2012 to over a trillion dollars in 2050. A medicine that could delay the onset of the disease was estimated to reduce the cost of care of Alzheimer's patients in 2050 to all payers by $447 billion.[15]

[15] Alzheimer's Association, "2012 Alzheimer's Disease Facts and Figures" (2012). Figures based on model developed for the Alzheimer's Association by The Lewin Group. Available at http://www.alz.org/documents_custom/trajectory_appendix_b.pdf

Spotlight on Therapies Targeting Diseases with No Recently Approved Therapies: Recent Progress Against Lupus

Lupus is a serious, potentially fatal autoimmune disease that attacks healthy tissues and presents as swelling in the joints, light sensitivity, fever, chest pain, hair loss, and fatigue. The Lupus Foundation of America estimates that 1.5 million Americans have a form of lupus. This complex disease can affect multiple organ systems, and symptoms can range in severity from day to day.[1] The complexity and heterogeneity of lupus present challenges in developing and evaluating potential new therapies, and at least seven drugs in the last several years have suffered setbacks in clinical trials.[2] Successful treatment of lupus will require an arsenal of safe, effective, and tolerable treatments, and the approval of belimumab (Benlysta®) is a significant step toward reaching that goal. As of December 2011, there were 58 other projects in development to treat lupus or various aspects of lupus such as serious kidney complications.

[1] FDA News Release, "FDA Approves Benlysta to Treat Lupus: First New Lupus Drug Approved in 56 Years" (9 March 2011). Available at http://www.fda.gov/newsevents/newsroom/pressAnnouncements/ucm246489.htm; Accessed on 07/24/12.

[2] Andrew Pollack, "Benlysta, a Lupus Drug, Is Approved by the FDA," New York Times (9 March 2011).

In ***cancer,*** many tumor types have proved resistant to existing drug therapies, but an improved understanding of the molecular nature of these diseases is being translated into potential new medicines. For ***ovarian cancer***, for which the last FDA-approved therapy was in 1996, there were over 120 potential NMEs in development, including 16 in Phase III, as of December 2011. 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 ***small cell lung cancer (SCLC)***, there were 22 and 34 NMEs, respectively, then in clinical development. Medicines in development include those that would make other treatments more tolerable for patients and personalized medicine approaches.

There are also a range of 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 under way to address various potential bioterrorism agents, which may cause death or disease in humans, animals, or plants. While the most recently FDA-approved treatment for ***anthrax,*** a highly dangerous, potential bioterrorism agent, was in 1987, there are now a dozen potential NMEs in development, one of which was just approved by the FDA.

For ***post-traumatic stress disorder (PTSD)***, existing therapies to treat anxiety and other symptoms have been found to help alleviate symptoms but there remains a need for therapies to treat the full spectrum of symptoms. There are only two therapies approved to specifically treat PTSD, with the most recent therapy approved in 1992. There were five potential NMEs in clinical development.

While a comprehensive, systematic total of potential medicines in development in areas that have not experienced an approval (either an NME approval, or a new indication approval for an existing medicine) in the past 10 years is not feasible with the existing dataset, Figure 7 presents figures totaling more than 400 projects that were in preclinical or clinical development for a subset of 15 diseases reviewed.[16]

[16] The 404 projects are composed of 150 Preclinical/Research Projects, 96 Phase I projects, 133 Phase II projects, and 25 Phase III projects.

Figure 7. Projects for Selected Diseases and Conditions with No Approvals in 10 Years

Indication	Total Projects
Amyotrophic lateral sclerosis (ALS)	61
Anthrax	27
Cervical cancer	28
Cholera	3
Lyme disease	3
Myasthenia gravis	7
Ovarian cancer	158
Post-traumatic stress disorder	8
Scleroderma (systemic sclerosis)	10
Septic shock	26
Sickle cell disease	19
Small cell lung cancer (SCLC)	41
Testicular cancer	4
Toxoplasmosis	2
Vascular dementia	7
Total Projects	404

E. Personalized Medicines in Development

Much has been written about the promise of "personalized medicines" – therapies tailored to the characteristics of specific types of patients. While the concept behind personalized medicine, tailoring an individual's treatment to his or her specific characteristics, is a long-standing goal in the practice of medicine, recent scientific advances are now making it possible to use "an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease."[17]

The FDA now lists 100 medicines with approved pharmacogenomic biomarkers in their drug labels.[18]

As an example, trastuzumab (Herceptin®), a targeted therapy first approved in September 1998 for the treatment of patients with a specific subset of aggressive breast cancer, was the first approved personalized medicine relying on a molecular diagnostic test to identify patients who would benefit from treatment. It is indicated for patients whose tumors overexpress the protein Human Epidermal Growth Factor Receptor 2, or HER2, which can make cancer cells grow and divide faster, resulting in a particularly aggressive form of breast cancer.

[17] National Human Genome Research Institute, National Institutes of Health, Talking Glossary of Genetic Terms, http://www.genome.gov/glossary/index.cfm?id=150&textonly=true; Accessed 03/19/12.

[18] See http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.html.

Like many personalized medicines, trastuzumab is a *targeted therapy* in that it is designed to target cells with specific receptors, rather than designed to destroy cells indiscriminately, as do conventional radiation or chemotherapy, which attack both healthy and diseased cells.

In terms of the pipeline of drugs in development, Figures 8 and 9 summarize the results of a separate prior analysis of late-stage clinical trials (i.e., Phase III and Phase IV) involving the use of molecular biomarkers (characteristics that can guide treatment and diagnosis and are integral to personalized medicine), by therapeutic area.

Rather than being performed on the same database described elsewhere in this report, which does not systematically capture biomarker or other indicators of a personalized medicine approach, this earlier analysis was performed using data in Clinicaltrials.gov via a two-step process: a key word search, followed by an individualized review. The analysis reflected all clinical trials listed in Clinicaltrials.gov as having been initiated on or before January 7, 2009, which were conducted in the United States, and which were classified as Phase III or IV (meaning only some clinical trials, those which were Phase III or IV as of that date, were reflected in the search). Late-stage trials that were reviewed as molecular biomarkers may not be defined until later in the development process, and so some personalized approach activity occurring earlier would have been excluded. The key word search identified possible personalized medicine clinical trials, and the resulting clinical trials were reviewed individually to confirm that they were truly personalized medicine trials.[19]

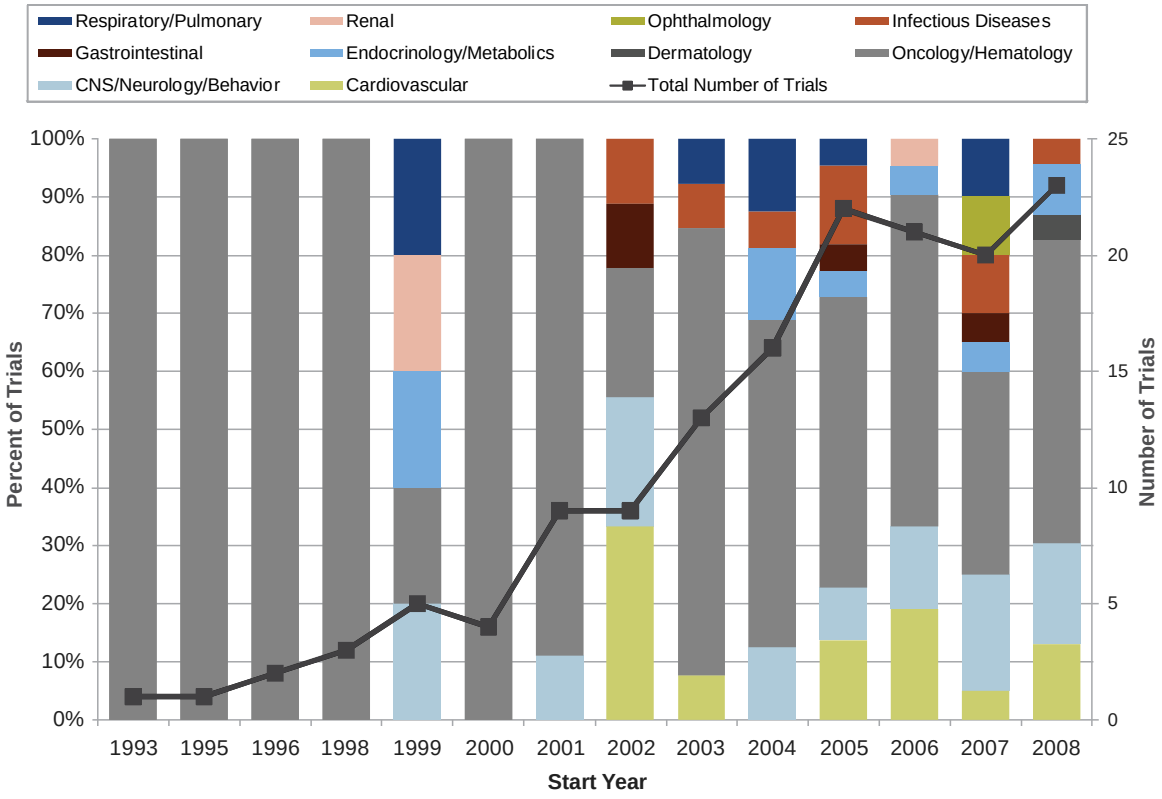
[19] Key words included the following terms: biologic marker biomarker, markers, signature molecule, overexpression, overexpress, overexpressing, expression, expressed, expressing, mutation, DNA alteration, gene alteration, genetic alteration, genetic chance, molpath.mut, mutated, mutations, sequence alteration, genotype, genotyping, receptor, genetic, express, and snp, single nucleotide polymorphism, snp info.

Figure 8. Personalized Medicine Trials by Condition and Therapeutic Area, 1993 to 2008

		Number of Trials	
Therapy Area	**Condition**	**N**	**%**
Cardiovascular	Coronary Disease/Dyslipidemia	6	4%
	Familial Hypercholesterolemia	7	5%
	Other	3	2%
CNS/Neurology/Behavior	Addiction	5	3%
	Alzheimer's Disease	4	3%
	Depression/Schizophrenia	8	5%
	Other	3	2%
Dermatology	Cutaneous Sarcoidosis	1	1%
Endocrinology/Metabolics	Pompe Disease	2	1%
	Other	6	4%
Gastrointestinal	Gastrointestinal	3	2%
Infectious Diseases	Hepatitis	3	2%
	HIV	4	3%
	Other	3	2%
Oncology/Hematology	Breast Cancer	48	31%
	Colorectal Cancer	4	3%
	Hemophilia	3	2%
	Lung Cancer	7	5%
	Prostate Cancer	3	2%
	Other	20	13%
Ophthalmology	Macular Degeneration	2	1%
Renal	Renal Disease	3	2%
Respiratory/Pulmonary	Asthma	7	5%
	Total	**155**	**100%**

Source: D. Nellesen et al., "Personalized Medicine: Trends in Clinical Studies Based on National Registry Data," poster presented at ISPOR, Orlando, Florida, May 2009. Available at: http://www.analysisgroup.com/personalized_medicine_trends

Figure 9. Distribution of Personalized Medicine Clinical Trials by Therapeutic Area and Growth Over Time, 1993 to 2008



Source: D. Nellesen et al., "Personalized Medicine: Trends in Clinical Studies Based on National Registry Data," poster presented at ISPOR, Orlando, Florida, May 2009. Available at: http://www.analysisgroup.com/personalized_medicine_trends

The number of clinical trials that are considered personalized has increased rapidly from the original trials of trastuzumab in breast cancer, increasing from two trials in 1996 to 22 trials in 2008. While cancer has been at the leading edge, more recently other therapeutic areas have seen personalized medicine approaches, including cardiovascular disease, infectious diseases, and respiratory disease. Breast cancer was the focus of approximately one-third of all personalized medicine trials included in the analysis since 1993. In 2008, the most recent year of the analysis, over half of personalized medicine trials focused on oncology/hematology, and approximately 12 percent of trials targeted cardiovascular disease. There were two trials in respiratory disease in 2007, and three trials in infectious diseases between 2007 and 2008.

Biopharmaceutical companies are increasing their emphasis on personalized medicine approaches – a 2010 survey by the Tufts Center for the Study of Drug Development found that 94 percent of the companies surveyed reported they were investing in personalized medicine research, and 12 to 50 percent of compounds in the development pipeline were described as personalized medicines.[20] Respondents

[20] Tufts Center for the Study of Drug Development, "Personalized Medicine Is Playing a Growing Role in Development Pipelines," *Impact Report* 12 (November/December, 2010): 6.

estimated a 50 percent increase in spending on personalized medicine between 2010 and 2015; as a result, the numbers reported above likely have grown since 2008.

Spotlight on Recent Personalized Medicines: Melanoma, Lung Cancer, and Cystic Fibrosis

Recently, three personalized medicines have emerged from the development pipeline and received FDA approval. Vemurafenib (Zelboraf®), crizotinib (Xalkori®), and ivacaftor (Kalydeco®) bring new treatment options for patients with melanoma, lung cancer, and cystic fibrosis, respectively.

Each of these drugs is indicated for patients expressing a specific genetic mutation where the drug is known to be effective. Prior to receiving one of these drugs, patients would be genetically tested to determine if the drug was appropriate for their specific form of the disease. In the case of ivacaftor, an appropriate cystic fibrosis genetic test was already available, while for vemurafenib and crizotinib, a companion diagnostic test was developed in conjunction with the drug and approved by the FDA simultaneously.

F. Novel Scientific Strategies

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***, which are 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. The FDA has now approved more than 30 monoclonal antibody drugs treating immunological diseases and various cancers.

Therapeutic cancer vaccines are another area in which there have been significant scientific breakthroughs in recent years. Unlike traditional vaccines, therapeutic vaccines harness the immune system to fight disease rather than to prevent it. Because tumors may undergo many adaptations and remain undetected by the immune system, scientists hypothesized that the body's natural defenses have the potential to fight cancer.

In April 2010, sipuleucel-T (Provenge®) became the first example of an FDA-approved therapeutic cancer vaccine. It is indicated for treatment of advanced asymptomatic or minimally symptomatic prostate cancer that is resistant to standard hormone treatment. Prostate cancer is the second most common type of cancer among men in the United States, after skin cancer, with approximately 240,000 newly diagnosed men in 2011. Of these, 4 percent will reach advanced prostate cancer, which has an estimated five-year survival rate of only 29 percent. The new therapy provides an additional treatment option for men with advanced prostate cancer. Current clinical evidence suggests that it can extend survival by about four months with relatively mild side effects. There were more than 20 more therapeutic cancer vaccines in development.

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

- ***Antisense RNA interference (RNAi) therapy,*** which operates in cells to silence gene expression, has advanced from the bench to the bedside in just 20 years. While most medicines target proteins such as enzymes and cellular receptors, these therapies open a new category of potential drug targets in the form of RNA, which carries the genetic information to create proteins. The therapeutic approach involves a synthesized strand of nucleic acid that binds to the messenger RNA produced by the gene, inactivating it. Two RNAi targeted therapeutics have received FDA approval, and there were more than 127 projects in the clinical research pipeline using this approach, including 12 projects in Phase III or later, with many more in preclinical research.
- ***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.
- ***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.
- ***Conjugated monoclonal antibodies*** are monoclonal antibodies that are joined to a cytotoxic agent that utilizes the selectivity of the antibody to deliver the cytotoxic 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.
- ***Transgenic products,*** drugs generated in genetically engineered animals, have already supplemented the conventional methods of obtaining blood factors through volunteer blood donations. Researchers are pursuing strategies to generate other pharmaceutically beneficial products.

As of December 2011, there were at least 577 projects in clinical development and 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 10. Examples of Selected Breakthrough Scientific Strategies

	Number of Projects by Phase				
	Phase I	Phase II	Phase III	U.S. Filed / Approved But Not Yet Marketed	Total Projects
Antisense therapies	63	52	10	2	127
Cell therapy	96	124	23	2	245
Gene therapy	35	50	12	2	99
Monoclonal antibody (conjugated)	63	31	8	-	102
Transgenic product	3	1	-	-	4
Total Projects	260	258	53	6	577

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: Authors' calculations, using EvaluatePharma data.

Spotlight on Breakthrough Scientific Strategies to Address Disease: RNA interference (RNAi) and Gene Therapy

RNAi Targeted Therapy Approach for Duchenne Muscular Dystrophy

Several RNAi therapies in clinical trials have shown potential in treating certain neuromuscular disorders such as Duchenne Muscular Dystrophy (DMD). DMD is a genetic disorder affecting approximately one in every 3,500 newborn boys, and is the most severe form of childhood muscular dystrophy.[1] Children with the disorder typically lose their ability to walk by their early teens and die in their early twenties. DMD is caused primarily by deletions in DNA within the gene that encodes for dystrophin, a structural protein found in normal muscle. These deletions ultimately cause muscle fibers to disintegrate faster than they can be regenerated. One medicine in development targets restoration of the function of dystrophin, and early clinical trials demonstrated improved dystrophin expression, as well as improvement in patients' ability to walk. As researchers begin to better understand the mechanisms behind RNAi targeted therapies, this approach may have implications for other disease areas.

Gene Therapy as a Possible Approach for Parkinson's Disease

Gene therapy is being studied by researchers as a potential approach to a number of different diseases and conditions, including Parkinson's disease, certain cancers, and HIV. The approach includes inserting genes into cells, via viruses that have been altered to make them safe for patients, in order to change the impact of genes that encode proteins involved in a particular disease. These genes might alter or replace a mutated gene or produce a new therapeutic protein. For instance, in the case of Parkinson's disease, there are a number of treatments addressing the disease's symptoms, but none that replace the lost nerve cells resulting from Parkinson's, or that would stop disease progression. One gene therapy in clinical trials uses an adeno-associated virus (AAV) as a vector to deliver neurturin to restore cells damaged in Parkinson's patients and to protect them from further degeneration.

[1] Centers for Disease Control and Prevention, Prevalence of Duchenne/Becker Muscular Dystrophy Among Males Aged 5--24 Years, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5840a1.htm

CONCLUSION

While it is impossible to predict which of the specific projects and products in development today will eventually proceed all the way to use by patients, today's pipeline of new medicines in development reflects diverse clinical research programs across many different therapeutic areas. The pipeline addresses both common conditions like cardiovascular disease and rare diseases like cystic fibrosis. Candidate medicines take varied scientific approaches, from novel therapies that target proteins in the body in new ways to drugs that work on never-before-targeted molecules, such as RNA or mRNA. Together, they have the potential to benefit many different patient populations and subpopulations.

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 new hope for current and future patients.

APPENDIX A: METHODOLOGY, DEFINITIONS, AND SOURCES

Except where otherwise noted, data were obtained from EvaluatePharma, a proprietary commercial database with coverage of over 4,500 companies and approximately 50,000 marketed and pipeline products (including those on-market, discontinued, and in development), and containing historical data from 1986 onward. 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 December 12, 2011.

While our interest is in 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, 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.

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 that would be granted a five-year period of 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. 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.

A ***New Derivative*** is defined as a product that is a new derivative of an existing product.

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 must have a 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.

Other data sources used include ClinicalTrials.gov, accessed on January 7, 2009, and the FDA Orphan Drug Product designation database, accessed on October 20, 2011.

APPENDIX B: 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
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	Diabetes
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

Therapeutic Area	Indication
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.