

The Biopharmaceutical Pipeline:

Evolving Science, Hope for Patients

The biopharmaceutical pipeline of new medicines contains a stunning range of innovative new treatment approaches that have the potential to save lives and improve patient health. A new report by Analysis Group, "Innovation in the Biopharmaceutical Pipeline: A Multi-Dimensional View," examines the pipeline from several different angles to capture the breadth and focus of ongoing research and to describe the array of potential new treatments and cures for patients. Across several measures of "innovativeness," the report found:

- Many novel scientific strategies are opening up new possibilities for fighting disease.
- Potential first-in-class medicines make up 70% of the pipeline.
- Nearly three times as many drugs for rare diseases and conditions are in the pipeline compared with a decade ago.
- Researchers are actively studying diseases and conditions with no recent approvals such as ALS, ovarian cancer, and septic shock.
- Personalized medicines are a growing proportion of the pipeline.

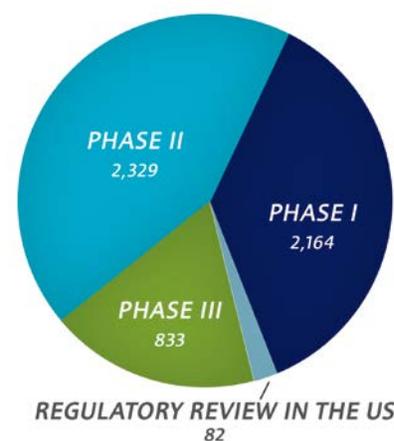
The analysis found that more than 5,000 potential new medicines – which may become available to U.S. patients – are in the pipeline globally – in large part funded by the more than \$500 billion invested in research and development (R&D) since 2000 by PhRMA member companies. These promising candidates build on the more than 300 medicines that have been approved by the FDA in the last decade.

Innovative medicines have improved quality of life, increased life expectancy, and enhanced productivity for millions of Americans. They have brought tremendous value to the U.S. health care system and the economy more broadly. But more progress is needed to address the most costly and challenging diseases and conditions facing patients in America and across the globe.

This paper takes a closer look at the biopharmaceutical pipeline and the Analysis Group report findings.

MEDICINES IN DEVELOPMENT BY REGULATORY PHASE

A Total of 5,408 Medicines Are Currently in Clinical Development



As many of the 5,408 medicines in development are in trials for more than one indication, the total number of projects in development is close to 8,000 as of December 2011.

MEDICINES IN DEVELOPMENT FOR SELECTED THERAPEUTIC AREAS

Therapeutic Area	Total Projects
Cancer (total)	3,070
Infections	750
Neurology	610
Immunology	298
Cardiovascular	450
Diabetes	281
Psychiatry	240
HIV/AIDS	185

"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."

— Analysis Group, *Innovation in the Biopharmaceutical Pipeline: A Multi-Dimensional View, 2013*

New Scientific Opportunities

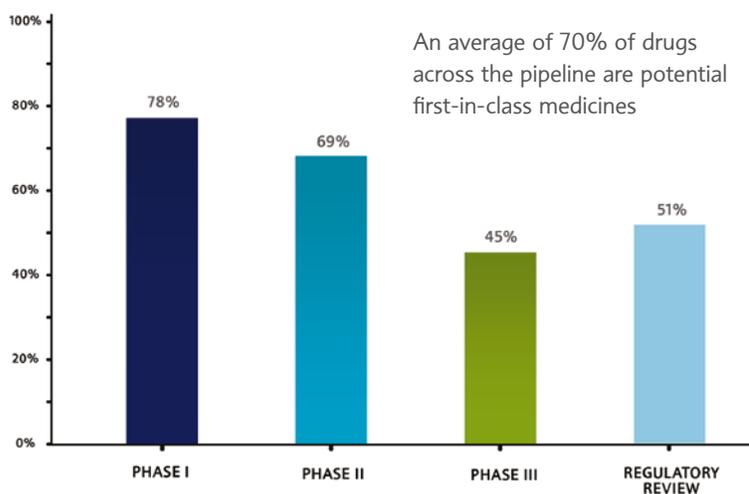
Biopharmaceutical researchers are continually exploring new scientific approaches to attack diseases in novel ways – resulting in unprecedented improvements in human health around the world. Today, the scientific opportunities available to researchers are quickly expanding. In particular, our growing understanding of the molecular and genetic bases of disease is opening up vast new avenues for developing targeted treatments that work more precisely and more effectively. Scientists did not have the tools to understand or target the underlying causes of many diseases just 15 or 20 years ago. Researchers are steadily applying this new knowledge to a range of different diseases and conditions.

Potential First-in-Class Medicines in the Pipeline

A first-in-class drug is one that uses a different mechanism of action from any other already approved medicine. Such medicines offer new treatment options for patients, particularly to patients who have not responded to existing therapies or for whom no existing treatment options are available. These medicines may improve the outlook for patients by providing greater efficacy, improved delivery, or fewer side effects. Subsequent medicines in the class may provide patients with different side-effect or efficacy profiles.

Across the entire clinical development pipeline, roughly 70% of projects are potentially first-in-class. While there may be more than one medicine in the pipeline with the same mechanism, it is difficult to predict which will be approved first. As illustrated in the figure below, high numbers of potential first-in-class medicines are seen in all phases of clinical development, but the percentage decreases for the later stages in part because medicines with new mechanisms are less likely to make it through the development process. First-in-class pipeline products may be expected to carry more clinical uncertainty than medicines using a "proven" mechanism of action, since there may be greater unknowns regarding their effect on both the disease and the human body. In spite of this, the proportion is still very high for Phase III candidates, with nearly half of all projects having the potential to lead to a first-in-class medicine.

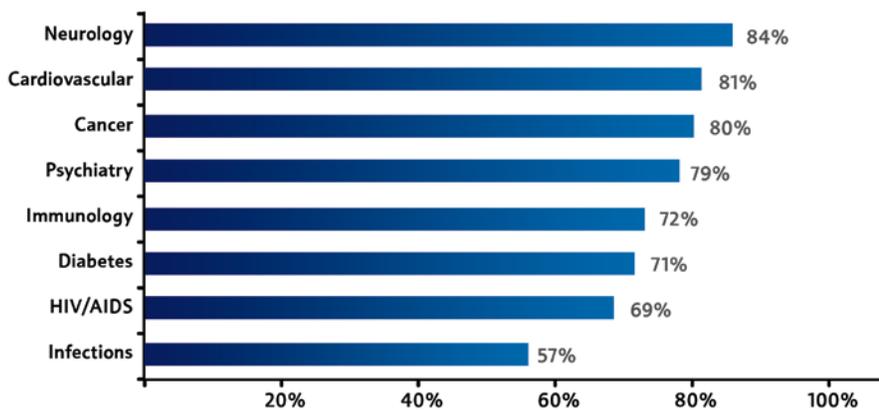
POTENTIAL FIRST-IN-CLASS MEDICINES BY PHASE



First-in-Class Medicines by Therapeutic Area

The percentage of projects in development which are potentially first-in-class is particularly high in neurology (84%), cancer (80%) and psychiatry (79%). The high proportion of potential first-in-class drugs in these disease areas reflects scientists' rapidly growing knowledge about the molecular underpinnings of these diseases. Researchers are increasingly able to define diseases and their mechanisms more clearly. For example, 100 years ago leukemia and lymphoma were considered to be one disease, but today the two encompass about 100 individual diseases. Other disease areas where new classes of medicines are particularly common include cardiovascular disease, immunology, and diabetes— all with well over half of the medicines in development being potentially first-in-class.

PERCENTAGE POTENTIAL FIRST-IN-CLASS MEDICINES IN SELECTED THERAPEUTIC AREAS

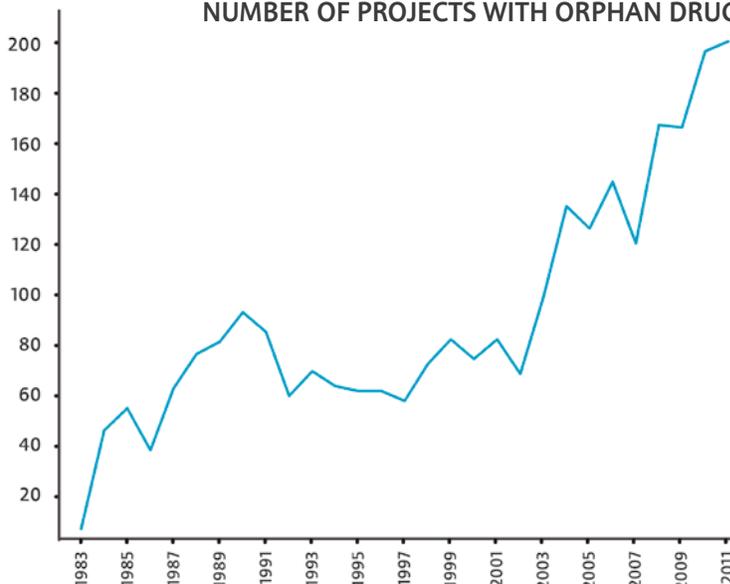


New Generation of Hepatitis C Medicines Increase Treatment Options

Options for hepatitis C patients have increased with recently approved medicines, and more progress is likely with newly discovered treatment mechanisms. An estimated 180 million people around the world have hepatitis C, a disease that attacks the liver and can lead to cirrhosis, liver cancer, and death. Two recently approved treatments mark a milestone as the first "direct-acting antivirals," which work by targeting specific enzymes of the hepatitis C virus. According to the Food and Drug Administration (FDA), these medicines significantly increase virologic response rates and may reduce treatment time, which is "a major step forward in the battle against chronic hepatitis C infection."

The 66 hepatitis C medicines currently in clinical trials in the U.S. promise to build on these advances. Many are direct-acting antivirals that target the virus in different ways. Some may reduce side effects and result in sustained improvements more quickly than was possible with existing therapies. According to experts, these drugs have the potential to eliminate the virus in "practically all patients."

NUMBER OF PROJECTS WITH ORPHAN DRUG DESIGNATION BY YEAR 1984-2011



Rare Diseases: The FDA designates medicines which treat rare diseases affecting fewer than 200,000 people "orphan drugs." There are nearly 7,000 rare diseases—many of which are serious or life-threatening and have few treatment options. Data demonstrate that recent advances have led to flourishing research in this area. In the last ten years the number of medicines in development with an orphan drug designation averaged 140 per year compared with 64 in the previous decade.



Therapies Targeting Diseases with Limited Options

Many new medicines are currently in development for diseases for which no new therapies have been approved in the last ten years. The Analysis Group researchers used this distinction to identify areas where patient needs are not fully met. This measure is imperfect, as some diseases may have had no new approvals because adequate treatments exist, while others may have had recent approvals but there remains a need for additional treatments. Nonetheless, it sheds a useful light on the scope of ongoing biopharmaceutical research focused on diseases where there is great need for new treatments. The table below illustrates some of these disease categories.

MEDICINES IN DEVELOPMENT FOR SELECTED DISEASES AND CONDITIONS WITH NO APPROVALS IN TEN YEARS

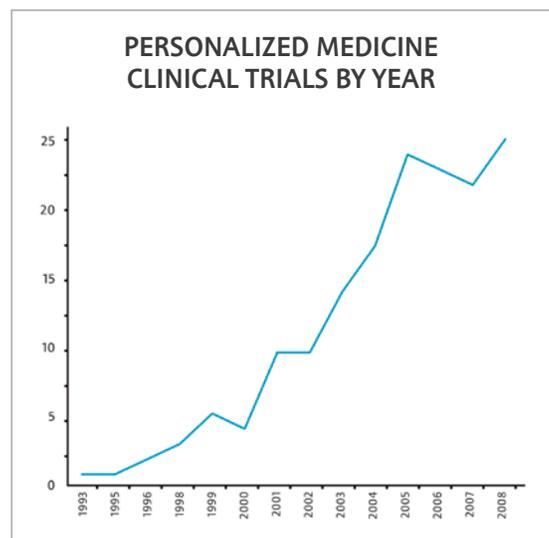
Therapeutic Area	Total Projects	Therapeutic Area	Total Projects
ALS	61	Ovarian cancer	158
Anthrax	27	Septic shock	26
Cervical cancer	28	Sickle cell disease	19
Myasthenia gravis	7	Small cell lung cancer	41

Drug Research Revived Thanks to Personalized Medicine

Personalized medicines have the potential to “revive” medicines in development that have not proven successful previously. When tested, some drugs may not benefit a broad population but may have a dramatic effect on particular subpopulations. An investigational product in development for gastric cancer initially appeared to have disappointing trial results. However, following a review of the data, researchers found that the investigational product provided benefit to a subset of patients whose (gastric) tumor expressed high levels of MET, a protein involved in cell growth. In that subset, the investigational product almost doubled survival rates by blocking a protein that activates MET. MET can contribute to cancer cell proliferation when the process goes awry. The investigational product is also being explored in the treatment of other cancers in which MET plays a similar role, including prostate cancer, colorectal cancer, and small cell lung cancer.

Personalized Medicine

Personalized medicine is becoming an integral part of the R&D process. This promising approach tailors treatments to the individual patient based on their molecular and genetic make-up, making it possible to more effectively prevent, diagnose and treat diseases. According to Analysis Group, biomarkers were found to be employed in 155 trials initiated before January 2009. The



report cites a 2010 Tufts Center for the Study of Drug Development survey of biopharmaceutical companies that found 12–50% of drugs in development were taking this targeted approach. The Tufts survey projects a sharp expansion in this area going forward as respondents anticipated a 50% increase in personalized medicine R&D investment between 2010 and 2015. With three new personalized medicines approved in 2011 and 2012, personalized medicine is beginning to bear fruit and offers great promise for patients.



Potential New Treatment for a Dangerous Mutation in Infants

Hypophosphatasia is a rare inherited bone disease that results from a genetic mutation which hinders the formation of bones and teeth and can result in substantial skeletal abnormalities. Severely affected infants often have persistent bone disease or die from respiratory insufficiency due to progressive chest deformity from poorly developed bones. Currently, there are no approved medicines for this disease. A potential therapy in development would provide the enzyme necessary for proper bone growth that those with hypophosphatasia are missing.

ALS: Fighting a Devastating Disease

ALS, or Lou Gehrig's disease, is a progressive neurodegenerative disease that causes the brain to lose control over body movement, ultimately resulting in paralysis and death. About 20,000-30,000 people suffer from ALS in the U.S. The one drug currently available to treat ALS can modestly slow progression of the disease, but new treatments are needed and researchers are working to deliver on the promise of growing scientific understanding. They are pursuing many new approaches to halt or slow the disease. Some approaches involve the use of the patient's own bone marrow stem-cells to create healthy neuron-like cells to replace diseased neurons. Other trials are studying ways to prompt the immune system to protect neurons affected by ALS.

Unraveling the Mysteries of Alzheimer's Disease

Alzheimer's is the 6th leading cause of death in the U.S., and its impact on patients and the health care system is growing. Existing medicines are able to treat the symptoms of the disease but cannot slow, prevent, or reverse the progressive dementia. Disease-modifying treatments that could delay the onset of the disease could reduce the cost of care of Alzheimer's patients in 2050 by \$447 billion.

Researchers continue to unravel the mysteries of the disease and are studying 125 new treatments in this area. Recent research has focused on the plaques and tangles which form in the brains of Alzheimer's patients and are thought to contribute to the death of nerve cells. One medicine in development has shown promise in reducing both brain plaques and tangles. A gene therapy also in clinical trials is being explored to restore lost neuron function. Researchers believe potential medicines like these may improve the outlook for patients.



"Just as the insights provided by genomics are one reason to feel optimistic, so is the progress scientists are making with new forms of medical intervention."

— *PwC Pharma 2020 Report, Nov 2012*

Novel Scientific Strategies

New scientific discoveries can open up broad possibilities for treating some of the most challenging diseases affecting patients. Molecular and biological targets that were beyond reach or completely unknown can become accessible with breakthroughs in basic science. The following five innovative platforms provide a glimpse of the scientific potential researchers are seeking to harness to fight the most challenging diseases:

- **Antisense RNA Interference (RNAi)** is a new strategy that targets RNA in order to silence gene expression. Whereas most drugs target proteins such as enzymes and cellular receptors, this new approach opens up RNA, which carries genetic information to create proteins, as a new potential target for drugs. Thus far, two RNAi therapeutics have been approved, and 127 more are in development.
- **Therapeutic Cancer Vaccines** harness the immune system to fight off disease that is already underway. The first therapeutic cancer vaccine was approved in 2010, and today 20 more are in development.
- There are 245 projects in development using **Cell Therapy**, 99 projects using **Gene Therapy**, and 102 projects using **Conjugated Monoclonal Antibodies** to target and kill tumors while sparing nearby healthy cells.

"We – you, me, all of us – will one day, for one reason or another, be a patient. When that day comes, we will all want access to the latest, best medicines available. Somewhere in American right now, there is a scientist hard at work, pushing the frontiers of research in pursuit of the next treatment that will take us from hope to cures."

— *John J. Castellani
President and CEO of PhRMA, 2013*

"Turning these promising compounds into effective treatments and cures requires the right public policies to preserve the environment in which innovation can flourish."

— *John Lechleiter, PhD,
Chairman, President, and Chief Executive Officer of Eli Lilly and Company
Forbes, 2012*



Monoclonal Antibodies (mAbs): A Successful Platform Technology

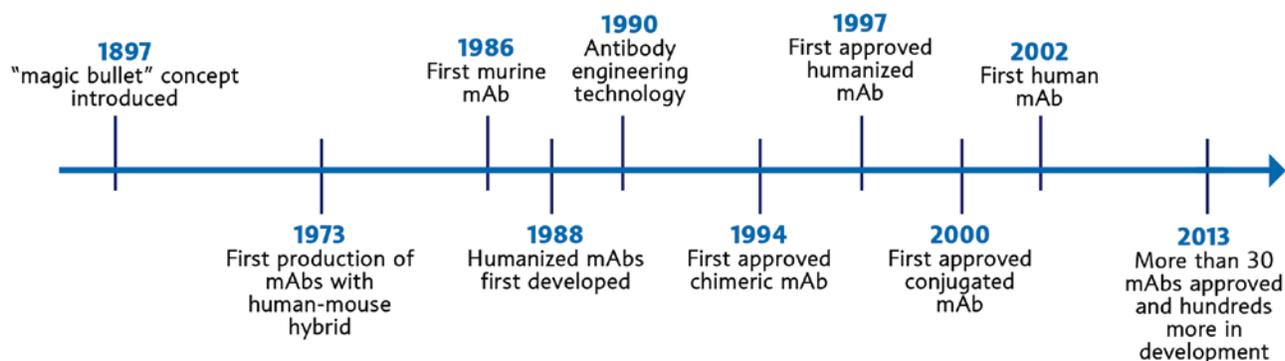
Antibodies are proteins that help the immune system identify foreign substances by binding to and marking them as foreign. As a result of scientific breakthroughs in the 1970s and 1980s, researchers began exploring mAbs as a therapeutic option. They focused first on identifying proteins only found on cancer cells that certain mAbs could specifically target and flag for the immune system to attack without harming healthy cells. This targeted approach has helped make it possible to fight cancer with fewer side effects.

By 2008, a total of 21 mAbs were approved in the U.S., and over 200 more were in the pipeline. Since 1996, the majority of new mAbs have treated various cancers and auto-immune

diseases such as arthritis and Crohn's disease. Many of these approved mAbs have proven over time to be effective in treating other diseases. For instance, drugs initially approved to treat immunological conditions were later found to be effective in treating various types of cancer.

Today researchers are creating 102 conjugated mAbs, a specific type of mAb that delivers disease-fighting compounds directly to diseased cells thanks to the specificity of mAbs. Thirty years after the initial development, the potential of mAb therapies to transform the treatment of very challenging diseases is still unfolding. The timeline below illustrates how our understanding of mAbs has grown over time, leading to new medicines.

MONOCLONAL ANTIBODY TECHNOLOGY ADVANCES OVER TIME



Conclusion

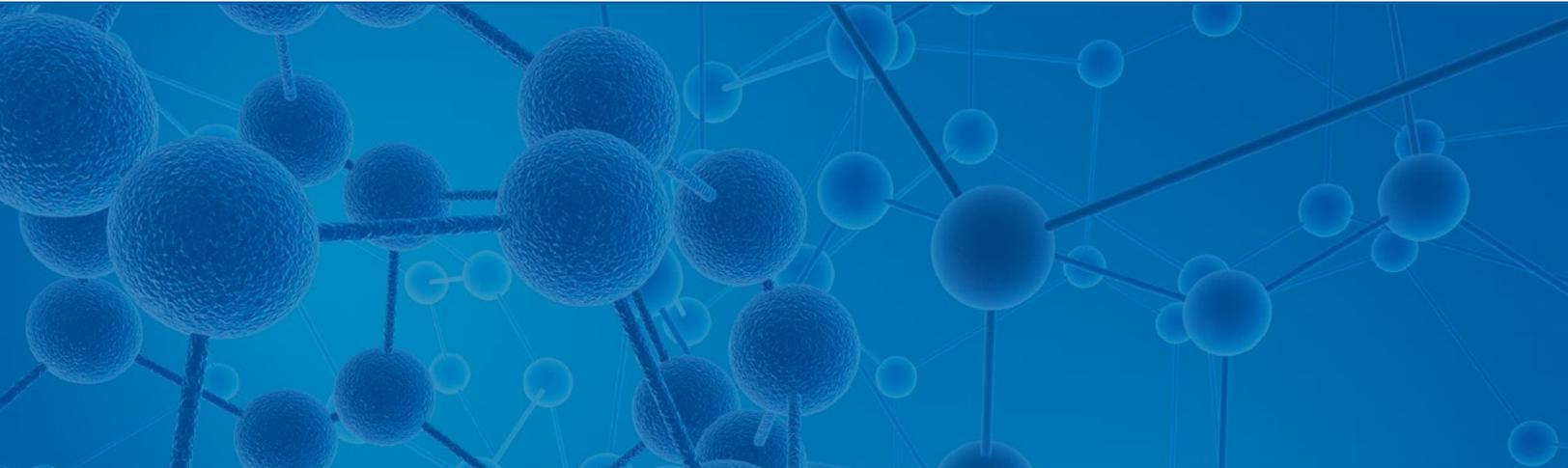
Today's pipeline of new medicines is vibrant and diverse. Biopharmaceutical innovation represents an important part of the solution to the health care challenges facing our nation. The continued discovery and development of new treatments saves and improves patients' lives. Supporting continued innovation and a thriving biopharmaceutical research sector requires a long-term view, with policies and regulatory structures that are consistent, predictable, and focused on patients' needs.

"Our progress in understanding the specific pathways of disease has identified hundreds of new targets for potentially life-saving drugs that hold the potential to treat individual patients much more effectively. The result of this understanding is an emerging paradigm shift for the development of new medicines."

— Mark McClellan, MD, PhD,
Brookings Institute Engelberg
Center for Health Care
Reform, 2012

Additional data are available in the Analysis Group report, "Innovation in the Biopharmaceutical Pipeline: A Multi-Dimensional View." Visit www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_pipeline.pdf

Related information available at www.PhRMA.org/pipeline



www.PhRMA.org

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