



REPORT TO THE PRESIDENT ON
PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT,
AND EVALUATION

Executive Office of the President
President's Council of Advisors on
Science and Technology

SEPTEMBER 2012





REPORT TO THE PRESIDENT ON
PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT,
AND EVALUATION

Executive Office of the President
President's Council of Advisors on
Science and Technology

SEPTEMBER 2012



About the President's Council of Advisors on Science and Technology

The President's Council of Advisors on Science and Technology (PCAST) is an advisory group of the nation's leading scientists and engineers, appointed by the President to augment the science and technology advice available to him from inside the White House and from cabinet departments and other Federal agencies. PCAST is consulted about and often makes policy recommendations concerning the full range of issues where understandings from the domains of science, technology, and innovation bear potentially on the policy choices before the President.

For more information about PCAST, see www.whitehouse.gov/ostp/pcast.



The President's Council of Advisors on Science and Technology

Co-Chairs

John P. Holdren

Assistant to the President for
Science and Technology
Director, Office of Science and Technology
Policy

Eric Lander

President
Broad Institute of Harvard and MIT

Vice Chairs

William Press

Raymer Professor, Computer Science and
Integrative Biology
University of Texas at Austin

Maxine Savitz

Vice President
National Academy of Engineering

Members

Rosina Bierbaum

Professor, Natural Resources and
Environmental Policy
School of Natural Resources and Environment
and School of Public Health
University of Michigan

S. James Gates, Jr.

John S. Toll Professor of Physics
Director, Center for String and Particle Theory
University of Maryland, College Park

Christine Cassel

President and CEO
American Board of Internal Medicine

Mark Gorenberg

Managing Director
Hummer Winblad Venture Partners

Christopher Chyba

Professor, Astrophysical Sciences and
International Affairs
Director, Program on Science and Global
Security
Princeton University

Shirley Ann Jackson

President
Rensselaer Polytechnic Institute

Richard C. Levin

President
Yale University

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

Chad Mirkin

Rathmann Professor, Chemistry, Materials
Science and Engineering, Chemical and
Biological Engineering and Medicine
Director, International Institute for
Nanotechnology
Northwestern University

Mario Molina

Professor, Chemistry and Biochemistry
University of California, San Diego
Professor, Center for Atmospheric Sciences
at the Scripps Institution of Oceanography
Director, Mario Molina Center for Energy and
Environment, Mexico City

Ernest J. Moniz

Cecil and Ida Green Professor of Physics and
Engineering Systems
Director, MIT's Energy Initiative
Massachusetts Institute of Technology

Craig Mundie

Chief Research and Strategy Officer
Microsoft Corporation

Ed Penhoet

Director, Alta Partners
Professor Emeritus, Biochemistry and Public
Health
University of California, Berkeley

Barbara Schaal

Mary-Dell Chilton Distinguished Professor of
Biology
Washington University, St. Louis
Vice President, National Academy of Sciences

Eric Schmidt

Executive Chairman
Google, Inc.

Daniel Schrag

Sturgis Hooper Professor of Geology
Professor, Environmental Science and Engineering
Director, Harvard University Center for
Environment
Harvard University

David E. Shaw

Chief Scientist, D.E. Shaw Research
Senior Research Fellow, Center for Computational
Biology and Bioinformatics
Columbia University

Ahmed Zewail

Linus Pauling Professor of Chemistry and Physics
Director, Physical Biology Center
California Institute of Technology

Staff

Deborah Stine

Executive Director

Amber Hartman Scholz

Assistant Executive Director

Danielle Evers

AAAS Science and Technology Policy Fellow

EXECUTIVE OFFICE OF THE PRESIDENT
PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY
WASHINGTON, D.C. 20502

President Barack Obama
The White House
Washington, DC 20502

Dear Mr. President,

We are pleased to send you this *Report To The President On Propelling Innovation In Drug Discovery, Development, and Evaluation*, prepared by the President's Council of Advisors on Science and Technology (PCAST). This report responds to your request for recommendations on this topic.

The past quarter-century has seen tremendous progress in biomedical research, leading to an increasing understanding of cancer, heart disease, diabetes, and other devastating diseases. The Nation has led the world in such progress, due in significant part to wise investments by the Federal Government in basic biomedical research. These breakthroughs are beginning to pay off in terms of new therapies for American patients.

Still, the pace of new therapeutic development has not kept up with the explosion in scientific knowledge. The number of novel drugs has remained constant for several decades, even as R&D budgets have substantially increased. As you know, this situation poses an increasing challenge for ensuring the creation of innovative therapies for patients. It is also causing serious stresses throughout the biomedical ecosystem.

To identify and develop constructive solutions to this challenge, PCAST engaged a wide range of stakeholders in discussions over the past twelve months—including senior leaders from the biopharmaceutical industry, patient advocacy groups, physician societies, and healthcare payors, as well as the senior leadership of the Food and Drug Administration and the National Institutes of Health.

There was broad recognition among these stakeholders that there are a wide range of issues that must be solved, only a minority of which are at the FDA. The stakeholders converged around a set of actions that the Federal Government and non-Federal parties can take to address this challenge. Informed by these discussions, PCAST has identified opportunities and made recommendations that are outlined in the attached executive summary and full PCAST report.

Together, the efforts that PCAST recommends are aimed at doubling over the next decade the rate of invention of innovative new medicines for patients, while increasing drug safety. PCAST believes the recommended actions will advance the health of Americans, as well as economic growth for the Nation.



John P. Holdren
Co-Chair



Eric Lander
Co-Chair



The President's Council of Advisors on Science and Technology

Executive Summary

Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation

Innovative Medicines Have Made Tremendous Contributions to Public Health

Biomedical innovations—including advances in medicines, medical procedures, and public health—have provided extraordinary benefits to the U.S. public. We live longer and we live healthier than our forebears. Life expectancy at birth has risen from around 47 years at the turn of the 20th century to 78 years today. Many diseases that were once fatal or debilitating can now be prevented, delayed, or ameliorated.

While nutrition, sanitation, other public health measures, and expanded access to care have been major sources of increasing human health, innovative medicines have also played a profound role in this progress. Infections that were the leading cause of mortality in the early 20th century are now largely eliminated. Vaccines have led to the eradication or control of many devastating infectious diseases, including polio, small pox, diphtheria, and measles. Pneumonia, the leading cause of death in the early 20th century, is now effectively treated with antibiotics. First recognized in 1981, HIV is now treated with over 20 Food and Drug Administration (FDA)-approved drugs, although more progress is still needed. Multi-drug regimens effectively control HIV infection, preventing the development of AIDS. Pharmaceutical therapies have led to cures for multiple malignancies that were once universally fatal; for example, childhood leukemia is now cured in 80 percent of cases, testicular cancer in over 90 percent of cases, and Hodgkin's lymphoma in over 90 percent of cases. Along with a reduction in smoking and better medical care, cholesterol-lowering therapy, blood-pressure-lowering drugs, anti-platelet agents, and diabetes treatment have contributed to a substantial decrease in death from heart attacks (70 percent decline over the past 60 years).

Innovation in Medicine Has Depended Upon a Thriving Ecosystem and Partnership Comprised of Researchers, Industry, and Regulators

These innovations have been brought forth by a remarkable ecosystem consisting of three major components: (1) academic researchers who have unlocked secrets of basic biology and revealed mechanisms that underlie disease, as well as the Federal and other funders who support their research; (2) a robust bio-pharmaceutical industry, which has developed molecules to treat disease and conducted clinical

trials to demonstrate their efficacy; and (3) government regulators, who have balanced the benefits and risks that are inherent in any medical innovation. The United States has consistently led the world in all these areas. Importantly, patients themselves have played a critical role in propelling advances by focusing attention on the urgency of developing therapies and spurring creative approaches, and by participating in clinical trials. Others including physicians, health care payers, pharmacists, and consumer groups have also played crucial roles. Medical progress depends on a successful partnership among these sectors.

We Stand at a Moment of Historic Progress in Biomedical Research with Extraordinary Promise for New Drug Development

The past quarter-century has seen stunning progress in basic biomedical research, propelled by powerful research technologies and revealing fundamental information about the biologic basis of disease. The opportunities for biomedical advances have never been brighter.

The tools for biomedical research have become dramatically more powerful. From 1990-2003, the Human Genome Project revealed the human genetic code and also propelled advances that have decreased the cost of sequencing a human genome by roughly one million-fold. A variety of technologies have made it possible to characterize, monitor, and understand far more of the underlying basis of physiology and disease. With these technologies, researchers are systematically discovering the genes and proteins that contribute to human diseases—including thousands of genes related to single-gene disorders (such as cystic fibrosis or Huntington’s disease), common polygenic diseases (such as diabetes and heart disease), and many cancers. These studies will lead to increasingly complete catalogs of disease causing entities over the next decade, providing a foundation for understanding disease.

By combining these powerful tools and information resources with basic biological and clinical studies, researchers have made remarkable progress in understanding the fundamental mechanisms underlying such fields as immunology, neurobiology, development, and cancer. Some of these discoveries have already been successfully translated into first-in-class drugs that are benefitting patients. An estimated 3,000 treatments are also in various stages of development, including more than 850 for cancer alone.

Despite These Advances, Pressing Needs Remain for Innovative Medicines and Cause for Concern About the Pace of Innovative Drug Development

Despite major breakthroughs for some diseases, many of the most common human diseases are not effectively treated by existing therapies. Many common malignancies, including lung cancer, colon cancer, breast cancer, and prostate cancer are incurable once they have metastasized. Ninety-six percent of orphan diseases, including rare cancers, lack effective therapies.¹ Despite current therapies, heart disease and stroke remain leading causes of mortality. Infectious diseases remain an important challenge with the emergence of antibiotic-resistant bacteria and multi-drug resistant tuberculosis, and the possibility of new viral pandemics that could cause widespread mortality. Psychiatric diseases remain a

1. Only 350 therapeutics are approved for 7000 rare diseases that cumulatively affect 30 million Americans. Accessed on May 14th, 2012.
www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm.

tremendous burden on society, and existing treatments have limited efficacy. Alzheimer's disease, which already afflicts more than 5 million people in the United States, at a direct cost of an estimated \$200 billion in 2012, including \$140 billion in Medicare/Medicaid payments, is increasing in prevalence as the population ages; some observers project that in the absence of new effective therapies the economic burden of Alzheimer's may ultimately exceed \$1 trillion per year.

The development of innovative medicines therefore remains essential for progress in the prevention and treatment of human disease. While biomedical research has experienced a golden age of progress over the past 25 years, there has been growing concern about the pace of translating scientific insight into public health impact. The many remarkable advances in basic biomedical research over the past quarter-century have not yet led to significant increase in the flow of new medicines to the American public.

The Innovation Ecosystem for Public Health is Under Significant Stress and R&D Productivity is Declining

Innovation in creating effective treatments for diseases that affect public health depends upon a complex ecosystem that involves basic biomedical research in universities and research institutes, clinical research in hospitals, and drug discovery and development in the biopharmaceutical industry. Each of the components of this ecosystem is under challenge.

Starting in 2003, Federal support for basic biomedical research failed to keep up with inflation (with the important exception of the major multi-year boost provided by the American Recovery and Reinvestment Act, which provided a significant increase in funds that has now ended). The prospects ahead are even more worrying, given the pressures on the Federal budget.

Similarly, clinical research has come under increasing pressure as the costs of clinical investigation and clinical trials increase and sources of financial support decline. NIH has recognized the importance of translating basic findings from "bench to bedside" through its Clinical and Translational Science Awards (CTSA) program, but this supports only a small portion of the Nation's clinical research and clinical trials infrastructure.

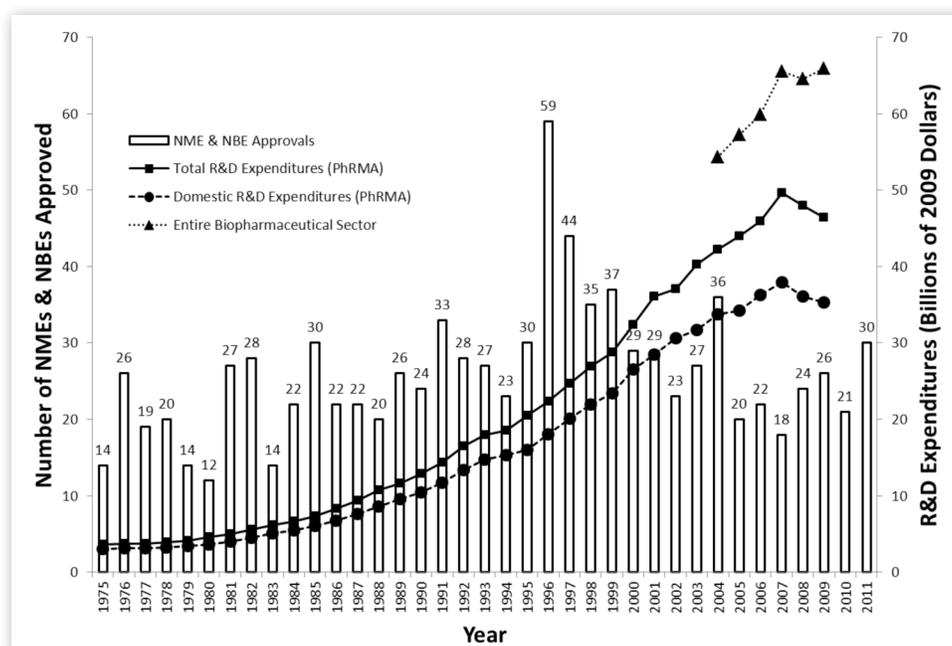
In addition, there is evidence that industry R&D investment, a major component of this innovation ecosystem, is under significant stress:

- The pharmaceutical industry is facing the largest "patent cliff" in its history: drugs with annual sales exceeding \$200 billion will come off patent in the period 2010-2014, resulting in a loss of more than \$100 billion in sales to generic substitutions; only a small fraction is expected to be replaced by new product revenues.
- Venture capital to start new biotechnology firms and fund innovative drug development activities appears to be declining, due not only to general economic conditions but to what are cited as concerns about unfavorable returns in the drug-innovation sector.
- Many companies are exiting important fields of critical public health need. For example, despite the growing health care and economic burden of neurodegenerative diseases, such

as Alzheimer’s disease and psychiatric diseases, many major pharmaceutical companies are closing down or severely curtailing drug discovery programs.

Despite dramatic advances in biological knowledge, the rate of new drugs applications and new drug approvals has remained relatively constant for several decades. While the output of new drugs has remained constant, total R&D investment by industry in drug discovery and development have grown exponentially, in inflation-adjusted terms (see figure below). As a result, the amortized R&D cost per newly approved drug has continued to grow.

FIGURE 1. Annual New Molecular Entity and New Biologic Entity Approvals vs. R&D Expenditures in 2009 Dollars.²



Key Challenges Affecting the Ecosystem for Innovative Medicines

There are two critical areas related to drug discovery and development that must be addressed to advance innovation:

- (1) Scientific knowledge gaps between basic research and commercial projects.** A fundamental problem is that advances in basic biomedical knowledge have not yet been matched by similar increases in the science and technologies needed for drug development. Accelerating the translation of biological insights into new medicines requires developing powerful new scientific knowledge, methodology, and tools. Academic scientists tend not to pursue such work, because it is seen as ‘too applied’ and because it often requires multi-disciplinary teams rather than individual academic labs. Companies tend to under-invest in such work because it is at least partially a ‘public good’—that is, a single company financing the development

2. Important caveats in the interpretation of this graph, and citation for the data are in the full report in Figure 1. (a).

of new foundational approaches to drug discovery cannot fully appropriate the fruits of the work, because much of it is disseminated to benefit all participants. Two key areas where such rate-limiting scientific knowledge gaps exist are: (1) predicting the efficacy and toxicity of candidate drugs to save time and investment that will ultimately not result in viable drugs, and (2) validating proteins in the human body as “druggable” targets to accelerate the development of candidate medicines.

- (2) Inefficiency in clinical trials.** Clinical trials constitute the largest single component of the R&D budget of the biopharmaceutical industry, at approximately \$31.3 billion, representing nearly 40 percent of the R&D budget of major companies. Unfortunately, there is broad agreement that our current clinical trials system is inefficient.

Currently, each clinical trial to test a new drug candidate is typically organized *de novo*, requiring substantial effort, cost, and time. Drug companies must identify clinical investigators and assemble multi-investigator teams. Protocols³ must be written and submitted to each of many institutions, and approval of these protocols can take several months without necessarily improving the ethics of the research or the protections afforded human subjects. Banking of biological specimens, which can be expensive and complex, is typically tailored to the short-term needs of an individual trial, rather than aimed at the long-term utility of large sample banks. Information technology is not standardized among trials. Navigating all of these requirements is challenging even for large pharmaceutical companies, and can be daunting for small biotechnology firms. Even in the best cases, the complexities add considerable time to trials—subtracting time from a successful drug’s eventual time on the market without competition.

Ultimately, the industry, the Federal Government, academic researchers, and the medical community would need to work collectively to fill such knowledge gaps and create efficient clinical trial networks and trial designs. The long-run return on these investments could be considerable to all contributors. The Nation would benefit from a coherent, high-level partnership that brings together high-level leadership from key stakeholders on a sustained basis to develop and help launch initiatives for shared scientific objectives, such as filling scientific knowledge gaps and building efficient clinical trial networks.

In addition to these two challenges facing the innovation ecosystem, economic incentives for certain areas of drug development important to public health may be insufficient to elicit adequate investment in innovation. Examples include antibiotics, where the public health need for innovation is high but potential market share and duration low, and Alzheimer’s disease, where the public health burden of the disease will vastly increase but the lack of basic understanding of the disease and the time and complexity of drug development discourages companies from investing. In these and other important areas where incentives are not aligned to encourage investment, it may be important to consider tools, such as vouchers for priority regulatory review, exclusivity periods, and targeted tax credits.

3. These are protocols developed by researchers who are using human subjects, and reviewed by respective Institutional Review Boards (IRBs) at academic centers and hospitals charged with overseeing compliance of research projects with regulations.

Key Challenges Related to Drug Evaluation

In addition to the issues facing drug discovery and development, critical challenges related to drug evaluation must be addressed to advance innovation to serve public health needs.

In principle, the FDA should ensure that the American people gain access as rapidly as possible to new drugs that are safe and effective, while ensuring that they are protected as completely as possible from drugs that are not. In practice, it is very difficult to strike this balance because our knowledge about safety and efficacy is often initially very limited and evolves over time. Approving drugs with too little information runs the risk of exposing the public to dangerous side effects or ineffective treatments. Requiring overly large and lengthy studies before approval runs the risk of delaying the availability of efficacious and potentially life-saving treatments. There are thus two ways in which the FDA can fail: by allowing unsafe medical products on the market, or by preventing patients from gaining timely access to innovative and potentially life-saving therapies. FDA must strike a balance between these two competing responsibilities.

PCAST found multiple issues and opportunities that related to the evaluation of new drugs for approval:

- (1) There are opportunities to accelerate the approval of a broader range of truly innovative drugs for patients who need them. Such acceleration should be supported by stronger tools for and enforcement of post-approval study.** Through the Accelerated Approval pathway developed in the early 1990s in response to the HIV/AIDS crisis, the FDA has authority to approve drugs for serious or life-threatening diseases on the basis of evidence that the drugs improve a surrogate endpoint reasonably likely to predict long-term clinical benefit to patients. The FDA could use its authority for a wider range of drugs and diseases than it does currently, by approving drugs on the basis of intermediate clinical endpoints (measures of how patients feel or function that are short of overall survival or irreversible morbidity). To support accelerated approval, it is important to strengthen the enforcement of requirements that drug sponsors investigate drugs' risks and benefits in the post-approval phase, and to ensure that FDA responds effectively to this knowledge. By law, the FDA now has authority to withdraw a drug's approval for a specific indication or for all indications. Yet once a drug is in wide use, it can be difficult in practice to remove it from the market.
- (2) The FDA requires methods to rapidly approve drugs for narrow populations for which there is a favorable benefit-risk balance, while protecting the broader population from drugs that have an unknown or unfavorable benefit-risk balance.** For many innovative drugs, it may be possible to demonstrate a favorable benefit-risk balance in certain groups of patients with serious manifestations of a disease or especially high risk of developing a disease long before it is possible to establish the benefit-risk balance for larger patient populations. Yet, once a drug is approved for one indication, physicians are permitted to prescribe off-label, for indications for which the drug has never been tested or in ways not recommended by the FDA. Off-label use has contributed to discoveries of useful applications of drugs to non-approved uses, but it can also pose serious risks to patients. To secure FDA approval for drugs that would benefit a narrow population, it is typically necessary to undertake extensive studies to determine the overall benefit-risk ratio to the broader population of patients who may use a drug. It would

be possible for the FDA to approve drugs for narrow indications based on limited development programs without broader studies, provided that the risk of widespread off-label use could be adequately mitigated. For such a pathway to be effective in constraining the use of certain drugs to certain patients, it would require a special designation that would strongly discourage prescribers from using these drugs off-label and discourage payors from reimbursing off-label use.

(3) Stronger post-marketing surveillance and communication tools are needed to generate evidence on the benefits and risks of drugs and to communicate those benefits and risks to the public.

The information available about a drug at the time of FDA approval is necessarily incomplete, because the patient population who receives the drug during clinical trials can differ in important ways from (and is substantially smaller than) the full patient population that can be prescribed a drug after it reaches the marketplace. These inherent uncertainties underscore the need to generate knowledge about a drug's risks and benefits over time as it is used more widely, in what is known as the "post-marketing phase." A drug might have benefits for diseases beyond the indication for which it was approved by the FDA, or it might have serious risks that outweigh its benefits. The FDA and public health agencies currently lack a robust and systematic way to track and monitor safety and effectiveness for most medical products in the marketplace. The Sentinel System for post-marketing surveillance currently under development by FDA holds the potential of becoming such a system, but has lacked adequate and sustained funding required to scale up and incorporate more data from electronic health records. In addition, while much of the public believes that FDA approved drugs are guaranteed to be safe and effective, there is no single moment at which a drug's full risks and benefits are known. The public would benefit from a greater understanding of the known risks and benefits and the uncertainty about drugs, and to know how this knowledge changes as a drug is in wider use in the population. The current tools for communicating the risks, benefits, and uncertainty about drugs are limited in their scope and effectiveness.

(4) Innovators require greater clarity about general regulatory pathways for innovative products and approaches.

For innovative drug developers to take on new approaches and new types of product areas, they need adequate clarity about the pathways and standards of evidence that the FDA will require in evaluating those products. In important emerging areas of science and innovation, the FDA will sometimes lack the resources and expertise to produce clear policies and standards in a timely enough manner to guide innovators in the development of such products. The development of rapid, clear, and thorough guidance documents that reflect the consensus of the scientific community on new and emerging areas of scientific innovation could help address this need. To develop such guidances in a timely manner while reflecting high-level expertise, the FDA may need to more heavily rely upon the biomedical community to collaboratively suggest standards and pathways that the agency can then consider in developing guidance documents to clarify its policies and practices.

(5) Innovators require greater consistency, efficiency, and communication with respect to their individual drug applications.

The interaction between individual drug sponsors and the FDA during the process of drug development and review is critical to efficient drug evaluation. Currently, this communication is constrained by formal requirements imposed by legislation.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

There is a need for strong project leaders at FDA with authority and accountability for resolving conflicts and who provide consistent and clear responses to sponsors throughout the drug development process (from the investigational stage through final consideration for approval). In addition, the FDA faces important management challenges, including antiquated IT systems and insufficient ability to assess management needs, pilot reforms, and ensure consistent implementation of programs and policies. This situation requires new mechanisms at the FDA for evaluating management needs, implementing new reforms, and ensuring accountability and consistency across the agency's centers and divisions.

High-Level Goal and Summary of Recommendations

PCAST recommends setting the following ambitious goal for the Nation:

Goal: Double the output of innovative, new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and government working together to decrease clinical failure, clinical trial costs, time to market, and regulatory uncertainty.

PCAST believes that achieving this goal is possible over the next 10-15 years, and that it will require active involvement and collaboration among stakeholders across multiple sectors. Various intermediate milestones toward the overall goal can be achieved more rapidly. Achieving the overall goal will require advances in: the science of drug development; the execution of clinical trials; the development pathways used for innovative medicines; the mechanisms for drug approval; surveillance and communication of risk; and management at the FDA.

PCAST makes eight important recommendations to unleash extraordinary innovation and investment in the service of public health. The full recommendations, contained in the attached full PCAST report, are extensive in their provisions. Here we briefly summarize some features of those recommendations.

Summary of Recommendations:

Improving Drug Discovery and Development

Recommendation 1: Support Federal Initiatives to Accelerate Therapeutics. The Federal Government should strongly support funding for basic biomedical research, and vigorously support the National Center for Advancing Translational Sciences (NCATS) at NIH and the Reagan-Udall Foundation (RUF).

Recommendation 2: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics. This high-level partnership should engage a range of stakeholders to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs. It should focus on identifying needs in three areas: (1) Filling key knowledge gaps in science, technology, and methodologies underlying drug discovery and development; (2) Improving clinical trials capabilities; and (3) Clarifying the development pathway for innovative medicines by convening the community to provide input to FDA on guidance documents.

Improving Drug Evaluation

Recommendation 3: Expand the Use in Practice of FDA's Existing Authorities for Accelerated Approval and for Confirmatory Evidence. The FDA should make full use of accelerated approval for all drugs meeting the statutory standard of addressing an unmet need for a serious or life-threatening disease, and demonstrating an impact on a clinical endpoint other than survival or irreversible morbidity, or on a surrogate endpoint, likely to predict clinical benefit. The FDA should also fully enforce its requirement for post-approval confirmatory studies demonstrating that the drug indeed results in desired long-term clinical benefit.

Recommendation 4: Create a New Pathway for Initial Approval of Drugs Shown to be Safe and Effective in a Specific Subgroup of Patients. This would be an optional pathway under which sponsors could propose early in the development process to study a drug for a narrow population. Such drugs would be approved under a designation of Special Medical Use, signaling strongly to payors and prescribers the limited population that should be prescribed a drug.

Recommendation 5: Explore Approaches for Adaptive Approval via Pilot Projects Under Existing Pathways but do not Create New Adaptive Approval Pathways through Legislation. The FDA should run pilot projects to explore adaptive approval mechanisms to generate evidence across the life-cycle of a drug from the pre-market through the post-market phase. Legislation to create a formal adaptive pathway or model for such approval, however, would be premature at this time, and PCAST advises against it.

Monitoring and Communication About Benefits and Risks

Recommendation 6: Improve FDA's Tools for Monitoring and Communication of Clinical Benefits and Risks. FDA should strengthen capabilities for post-marketing surveillance, and the Congress should authorize line-item appropriations of \$40M per year to expand the Sentinel System accordingly. The FDA should work with stakeholders to develop new tools to effectively communicate risks and benefits to patients and the broader public.

Improving FDA Management

Recommendation 7: Reform Management Practices at FDA. The FDA should implement a range of reforms, including the use of pre-market review leaders to oversee each drug candidate application from its investigational stage through final marketing decision. Other reforms should include establishing a regulatory innovation program, overhauling the IT systems, and establishing a Commissioner's Advisory Board for Medical Products to improve management and ensure consistent implementation of reforms.

Economic Incentives

Recommendation 8: Study Current and Potential Economic Incentives to Promote Innovation in Drug Development. The Secretary of HHS should commission a study of economic incentives to assess the utility of various types of incentives, determine whether current incentives are aligned to promote innovation generally and in specific areas of public health priority, and examine whether targeted changes to economic incentives would serve National needs.



The President's Council of Advisors on Science and Technology

*Report to the President on
Propelling Innovation in Drug Discovery,
Development, and Evaluation*



PCAST Drug Innovation Invited Experts

PCAST Members

Eric Lander

President
Broad Institute of Harvard and MIT

Christine Cassel

President and Chief Executive Officer
American Board of Internal Medicine

Richard C. Levin

President
Yale University

Ed Penhoet

Director, Alta Partners
Professor Emeritus, Biochemistry and Public Health, University of California, Berkeley

Invited Experts

Jeff Allen

Executive Director
Friends of Cancer Research

Jerry Avorn

Professor of Medicine
Brigham and Women's Hospital, Harvard Medical School

David Beier

Senior Vice President of Global Government Affairs, Communications, & Philanthropy
Amgen Inc.

Rob Califf

Director
Duke Translational Medicine Institute
Professor of Medicine
Vice Chancellor for Clinical Research
Duke University Medical Center

Mikael Dolsten

President
Worldwide Research and Development
Pfizer, Inc.

Laura Esserman

Director
Carol Franc Buck Breast Care Center
Professor of Surgery and Radiology
University of California, San Francisco

Ruth R. Faden

Wagley Professor of Biomedical Ethics
Director, Berman Institute of Bioethics
Johns Hopkins University

Mark Fishman

President
Novartis Institutes for BioMedical Research

Alan Garber

Provost
Harvard University

Garret A. FitzGerald

Professor of Medicine and Chair of Pharmacology, Director, Institute for Translational Medicine and Therapeutics
University of Pennsylvania

Kathy Giusti

Founder and CEO
Multiple Myeloma Research Foundation

Gigi Hirsch

Executive Director
Center for Biomedical Innovation and Program
Director, NEWDIGS

Charles Homcy

Venture Partner
Third Rock Ventures

Peter Barton Hutt

Senior Counsel
Covington & Burling LLP

Steven Jacobsen

Director of Research
Kaiser Permanente-Southern California

John C. Lechleiter

Chairman and Chief Executive Officer
Eli Lilly and Company

Freda C. Lewis-Hall

Chief Medical Officer and Executive Vice
President
Pfizer Inc.

Clive Meanwell

Chairman and Chief Executive Officer
The Medicines Company

Kenneth Oye

Associate Professor of Political Science and
Engineering Systems
Massachusetts Institute of Technology

Ed Pezalla

National Medical Director
Aetna

Frank J. Sasinowski

Director
Hyman, Phelps & McNamara Law Firm

Vicki Sato

Professor of Management Practice
Professor, Department of Molecular and Cell
Biology
Harvard University

Richard L. Schilsky

Professor of Medicine
Chief, Section of Hematology-Oncology
Department of Medicine, Biological Sciences
Division, University of Chicago

Stephen A. Sherwin

Chairman of the Board and Co-Founder
Ceregene, Inc.
Chairman Emeritus
Biotechnology Industry Organization

David Singer

Limited Partner
Maverick Capital Ltd.

Moncef Slaoui

Chairman, Research & Development
GlaxoSmithKline

Henry A. Solomon

Senior Medical Advisor and Chair of the
Professional and Corporate Consortium
American College of Cardiology

Sean Tunis

President and CEO
Center for Medical Technology Policy

Doug Williams

Executive Vice President, R&D
Biogen Idec

Elias Zerhouni

President, Global Research & Development
Sanofi

Federal Liaisons

Sandra L. Kweder

Deputy Director, Office of New Drugs,
Center for Drug Evaluation and Research
Food and Drug Administration

Amy P. Patterson

Associate Director for Science Policy
National Institutes of Health

Vicki L. Seyfert-Margolis

Senior Advisor and Director for Science
Innovation and Policy
Office of the Commissioner
Food and Drug Administration

Janet Woodcock

Director
Center for Drug Evaluation and Research
Food and Drug Administration

Staff

Amber Hartman Scholz

Assistant Executive Director, PCAST, OSTP

Michael Stebbins

Assistant Director for Biotechnology, OSTP

Advisor

Bina Venkataraman

Director of Global Policy Initiatives
Broad Institute of Harvard & MIT



Table of Contents

I. Introduction	1
Innovative Medicines Have Made Tremendous Contributions to Public Health	1
Innovation in Medicine has Depended on a Partnership Among Researchers, Industry, and Regulators	1
Despite Advances, There Remain Pressing Needs for Innovative Medicine	4
We Stand at a Moment of Historic Progress in Biomedical Research, with Extraordinary Promise for New Drug Development.	5
Yet There Are Reasons for Concern About the Pace of Innovative Drug Development.	7
Origin of this Study.	7
Scope of this Study.	8
II. Innovation Under Stress	9
New Drugs: Output Flat, Productivity Declining	10
Challenges in Drug Development	12
III. Improving Drug Discovery and Development	17
Gap Between Basic Research and Commercial Projects.	17
Inefficiency in Clinical Trials	20
Economic Incentives	24
IV. Improving Drug Evaluation	27
Improving Tools for Balancing Risk and Benefit.	28
Enhancing Regulatory Certainty for the BioPharmaceutical Industry as a Whole	41
Enhancing Regulatory Certainty for Individual Drug Development Plans	44
Management Issues at FDA	48
V: A Path Forward: Recommendations for Propelling Innovation in Drug Discovery, Development, and Evaluation	51

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

A. Improving Drug Discovery and Development	51
Recommendation 1: Support Federal Initiatives to Accelerate Therapeutics	53
Recommendation 2: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics	56
B. Improving Drug Evaluation	58
Recommendation 3: Expand the Use in Practice of FDA's Existing Authorities for Accelerated Approval and Confirmatory Evidence	61
Recommendation 4: Create a New Pathway for Initial Approval of Drugs Shown to be Safe and Effective in a Specific Subgroup of Patients	64
Recommendation 5: Explore Approaches for Adaptive Approval Via Pilot Projects Under Existing Pathways, but Do Not Create New Adaptive Approval Pathways Through Legislation.	67
Recommendation 6: Improve FDA's Tools for Monitoring and Communication of Clinical Benefits and Risks	70
C. Improving FDA Management.	70
Recommendation 7: Reform Management Practices at FDA	71
D. Economic Incentives	73
Recommendation 8: Study Current and Potential Economic Incentives to Promote Innovation in Drug Development.	74
E. Central Role for Patients and Physicians.	74
F. Timeframe for Action	74
G. Towards a National Innovation Strategy	75
Appendix A. Additional Experts Providing Input	77
Appendix B. Acknowledgments	81
Appendix C. Acroynms Used	83



I. Introduction

Innovative Medicines Have Made Tremendous Contributions to Public Health

Biomedical innovations—including advances in medicines, medical procedures, and public health—have provided extraordinary benefits to the U.S. public. We live longer and we live healthier than our forebears. Life expectancy at birth has risen from around 47 years at the turn of the 20th century to 78 years today.⁴ Many diseases that were once fatal or debilitating can now be prevented, delayed, or ameliorated.

While nutrition, sanitation, other public health measures, and expanded access to care have been major sources of increasing human health, innovative medicines have also played a profound role in this progress. Infections that were the leading cause of mortality in the early 20th century are now largely eliminated. Pneumonia, the leading cause of death in the early 20th century, is now effectively treated with antibiotics. Vaccines have led to the eradication or control of many devastating infectious diseases, including polio, small pox, diphtheria, and measles. First recognized in 1981, HIV is now treated with over 20 FDA-approved drugs, although more progress is still needed. Multi-drug regimens effectively control HIV infection, preventing the development of AIDS. Pharmaceutical therapies have led to cures for multiple malignancies that were once universally fatal; for example, childhood leukemia is now cured in 80 percent of cases, testicular cancer in over 90 percent of cases, and Hodgkin's lymphoma in over 90 percent of cases. Recombinant proteins, replacing specific proteins that are not effectively produced by individuals carrying certain genetic mutations, have transformed the therapies for multiple debilitating disorders including type I diabetes and hemophilia. Immunosuppressive drugs have offered effective therapies for autoimmune disorders, such as multiple sclerosis, and have enabled organ transplantation. Along with a reduction in smoking and better medical care, cholesterol-lowering therapy, blood-pressure-lowering drugs, anti-platelet agents, and diabetes treatment have contributed to a substantial decrease in death from heart attacks (70 percent decline⁵ over the past 60 years).

Innovation in Medicine has Depended on a Partnership Among Researchers, Industry, and Regulators

These innovations have been brought forth by a remarkable ecosystem consisting of three major components: (1) academic researchers who have unlocked secrets of basic biology and revealed mechanisms that underlie disease, as well as the Federal and other funders who support their research; (2) a robust bio-pharmaceutical industry, which has developed molecules to treat disease and conducted clinical

4. Arias E. United States life tables, 2007. National vital statistics reports; vol 59 no 9. Hyattsville, MD: National Center for Health Statistics. 2011. Accessed May 14th, 2012. www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_09.pdf.

5. Age-adjusted decrease from 589 age-adjusted deaths per 100,000 people in 1950 to 178.5 in 2010. 2010 data can be found in the most recent National Vital Statistics Report. Accessed May 14th, 2012. www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf. 1950 data can be found in the CDC's historical unpublished tables. Accessed May 14th, 2012. www.cdc.gov/nchs/nvss/mortality/hist293.htm#unpublished.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

trials to demonstrate their safety and efficacy; and (3) government regulators, who have balanced the benefits and risks that are inherent in any medical innovation. Patients themselves have played a critical role in propelling advances by focusing attention on the urgency of developing therapies and spurring creative approaches, and by participating in clinical trials. Medical progress depends on a successful partnership among these sectors. Others, including physicians, health care payors, pharmacists, and consumer groups, also play crucial roles.

The United States has consistently led the world in all these areas:

- (i) **Academic research.** By any measure, the Nation has been the world leader in groundbreaking biomedical research. This success is owed in large part to the strength of its extraordinary universities and research institutions. Federal investments in the biomedical research enterprise, led by the National Institutes of Health (NIH) and augmented by other agencies, have for the last 60 years propelled research advances by supporting a robust academic community that generates biomedical knowledge, patentable inventions, and trained scientists, including 135 NIH-funded Nobel Laureates.⁶ In 2010, Federal funding for health research totaled about \$46 billion (about \$35 billion from NIH, of which \$5 billion was provided under the Recovery Act⁷), while private and public health research funding combined reached \$140 billion.⁸
- (ii) **Biopharmaceutical industry.** The United States has also been an indisputable leader in the global biopharmaceutical industry. This leadership has resulted from a combination of factors, including: a strong patent system, access to capital, strong support for research and development (R&D) by both public and private funders, a high-quality science-based regulatory system at the Food and Drug Administration (FDA), and a market that recognizes and pays for innovative new medicines.

As of 2005, 8 of the world's top 15 pharmaceutical companies (by sales) were headquartered in the United States.⁹ Since the 1960s, the United States has been the headquarters for a larger share of firms that invent and introduce to market new chemical entities (NCEs) than any other country, and from 2001-2010, U.S.-based firms invented 57 percent of the NCEs produced globally.¹⁰ More than half of all clinical trials underway are being conducted in whole or in part in the United States.¹¹

In the last three decades of the 20th century, a revolution in molecular biology and associated technologies, including recombinant DNA, gave birth to a new industry, biotech. The biotech industry arose and has flourished in the United States, with strong early clusters in the high-tech

6. The NIH website lists winners of Nobel Prizes earned over the past 60 years. Accessed May 14th, 2012. www.nih.gov/about/almanac/nobel/.

7. Data from fiscal year 2010 can be found on the NIH databook. Accessed May 15th, 2012. report.nih.gov/nihdatabook/ Data on American Reinvestment and Recovery Act grants to NIH can be found on the NIH website. Accessed May 15th, 2012. grants.nih.gov/recovery/.

8. Overall health research spending includes the \$45.9 billion from federal sources, \$76.5 billion from industry, and \$18.1 billion from other sources. Accessed May 14th, 2012. www.researchamerica.org/uploads/healthdollar10.pdf.

9. This has stayed relatively constant since the 1970s, though U.S. firms had moved from the bottom to the top of the top-15 list by 2005, representing the top firms by 2005. <http://www.hbs.edu/research/pdf/09-118.pdf>.

10. The Milken Institute study uses NCEs as an indicator of biomedical innovation. Accessed May 14th, 2012. www.milkeninstitute.org/pdf/CASMIFullReport.pdf.

11. Ibid.

I. INTRODUCTION

and highly-educated areas near San Francisco and Boston, and subsequent expansion to other locations including Seattle, San Diego, North Carolina, Maryland, and Virginia. A unique combination of access to academic research institutions, scientists, and venture capitalists created the ripe conditions for the industry to take hold and grow from the 1980s to today, aided by supportive legislation, such as the Bayh-Dole Act, that encouraged universities and businesses to commercialize scientific discoveries in biotechnology. The United States accounts for more than 40 percent of the world's patents in biotechnology—far more than the E.U. at 25 percent and Japan at 17 percent.¹²

The Nation's leadership in biomedical innovation has been supported by a robust industry, and, in turn, investments in biomedical research and corresponding medical advances have allowed industry and the economy to thrive. Biomedical innovation has supported U.S. economic growth, and high-value, high-skilled jobs for Americans. The medical innovation sector as a whole (including the public and private enterprises) employs nearly one million people¹³ and industry-contracted studies show that exports in 2010 from the biopharmaceutical industry reached nearly \$47 billion, with a subset of the industry, biotechnology products yielding a net positive trade balance.¹⁴ This is a source of significant export strength relative to major industries, such as automobiles (\$38.4 billion in 2010 exports); plastics and rubber products (\$25.9 billion in 2010 exports); communications equipment (\$27 billion); and computers (\$12.5 billion). Pharmaceutical sales have increased steadily over the past decade,¹⁵ reaching a record high of \$856 billion in 2010. The biopharmaceutical industry estimates that it pays an average salary of \$96,563 to the 650,000 people it employs, and that it has indirectly contributed more than \$300 billion to U.S. GDP.¹⁶ Moreover, public health gains as a result of biomedical innovation bolster the U.S. economy; the growth in life expectancy between 1970 and 1990, for example, had added approximately \$2.4 trillion to the U.S. GDP by the year 2000.¹⁷

(iii) Food and Drug Administration. The Federal Government has also been at the forefront of protecting public safety, while promoting innovation. It has done so by maintaining a predictable, efficient, and transparent regulatory review process that affords patients timely access to safe and effective medicines. In 1906, when Congress enacted the first national Food and Drug Act and created the Bureau of Chemistry (the predecessor of the FDA) in 1906, medicines were developed and marketed in a “wild west” environment. Opium, heroin, and cocaine were sold without restrictions; circus performers sold medicinal products to their audiences; and medicines could be labeled as cure-alls, despite having undergone no tests and listing none of their ingredients. Over the past century, the FDA has become increasingly scientific and professional in its efforts to protect the health of U.S. citizens from unsafe and ineffective medical products.

12. 2008 OECD compendium of patent statistics. Accessed May 15th, 2012.

www.oecd.org/dataoecd/5/19/37569377.pdf.

13. Paying them wages totaling \$84B in 2008 according to Ehrlich, E. “An Economic Engine—NIH Research, Employment, and the Future of the Medical Innovation Sector.” 2011. Report sponsored by United for Medical Research.

14. U.S. Census Bureau. U.S. International Trade Statistics by NAICS codes. 2011.

15. CMR International, 2011. CMR International Pharmaceutical R&D Factbook. Thomson Reuters.

16. Archstone Consulting & R.L. Burns. Fact sheet cited in PhRMA profile. 2011.

17. Murphy, K. and Topel, R. “Diminishing returns? The costs and benefits of improving health.” *Perspect. Biol. Med.* 2003; 46: Suppl S108-S128.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

On the whole, Americans express confidence in the performance of the FDA.¹⁸ Standards set by the Agency, such as the requirement for well-controlled¹⁹ trials to demonstrate efficacy of new therapies, have helped improve the quality and public health benefits of drugs on the market.

A famous example of FDA's important role in protecting the public was its decision not to approve thalidomide²⁰ for marketing in the United States; the drug was given to pregnant mothers in Europe to prevent morning sickness and was later found to cause birth defects in thousands of newborns. In the 1960s and 1970s, on the heels of the thalidomide crisis, Congress changed the law to require a demonstration that drugs are effective in addition to being safe. In response, the FDA undertook a complete re-evaluation of the pharmacopeia to uphold the standard that products must demonstrate safety and efficacy. In important cases, the FDA has also responded to urgent medical needs by adopting innovative approaches to regulation. The best example was in the late 1980s and early 1990s, when the FDA created the Accelerated Approval pathway in response to the HIV/AIDS crisis, under which it rapidly approved drugs for serious or life-threatening diseases, based on their ability to affect "surrogate endpoints" (such as the amount of virus in the blood) rather than waiting for much-longer studies measuring clinical endpoints such as death. In the area of orphan and rare diseases, the Agency has demonstrated notable regulatory flexibility and innovation in order to get drugs to very small patient populations who suffer rare conditions.²¹ Between 1970 and 2011, the FDA approved 1046 new therapeutics—new molecular entities and new biologic entities (NMEs and NBEs)—for marketing in the United States.²²

Despite Advances, There Remain Pressing Needs for Innovative Medicine

Despite major breakthroughs for some diseases, many of the most common human diseases are not effectively treated by existing therapies. Many common malignancies, including lung cancer, colon cancer, breast cancer, and prostate cancer, are incurable once they have metastasized. Ninety-six percent of orphan diseases, including rare cancers, lack effective therapies.²³ Despite current therapies, heart disease and stroke remain leading causes of mortality. Infectious diseases remain an important challenge with the emergence of antibiotic-resistant bacteria and multi-drug resistant tuberculosis, and the possibility of new viral pandemics that could cause widespread mortality. Psychiatric diseases remain a tremendous burden on society, and existing treatments have limited efficacy. Alzheimer's disease, which already afflicts more than 5 million people in the United States at a direct cost of an estimated \$200

18. According to a recent survey conducted by Research America, 72 percent of Americans say they are very confident or confident in the FDA's safety review system. Accessed May 14th, 2012. www.policymed.com/2010/05/research-america-study-americans-confident-in-fda-and-biomedical-research.html.

19. The standard applied to many new drugs is evidence from two randomized controlled trials, though there are important exceptions.

20. Avorn, J. "Learning about the safety of drugs—a half century of evolution." *N. Engl. J. Med.* 2011; 365: 2151.

21. A recent analysis of 135 non-cancer orphan drug approvals between 1993 and 2012 indicated that 90 of these approvals demonstrated "regulatory flexibility" either in terms of administrative discretion or "case by case" flexibility. Sasinowski, F. "Quantum of effectiveness in FDA's approval of orphan drugs." *Drug Inf. J.* 2012; 46: 238. DOI: 10.1177/0092861511435906.

22. FDA data from the Center for Drug Evaluation and Research to PCAST in response to request.

23. Only 350 therapeutics are approved for 7000 rare diseases that cumulatively affect 30 million Americans. www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm239698.htm.

I. INTRODUCTION

billion in 2012, including \$140 billion in Medicare/Medicaid payments, is increasing in prevalence as the population ages; some observers project that in the absence of new effective therapies the economic burden of Alzheimer's may ultimately exceed \$1 trillion per year.²⁴

While there are many opportunities to improve public health by better deploying existing approaches (including wider use of existing drugs, prevention strategies, behavioral modifications, and other public health measures), even perfect use of existing solutions would not prevent cancer or heart disease from being leading causes of mortality, and would not eliminate the burden of a host of diseases. The development of innovative medicines therefore remains essential for progress in the prevention and treatment of human disease.

It is sometimes argued that medical innovation is part of the fundamental problem with the U.S. health-care system, because innovation drives up costs. We disagree with this reasoning. In the long run, medical innovation is one of the best ways both to save lives and to decrease dramatically the economic costs of disease: antibiotics now cost pennies a dose, the polio vaccine is much cheaper than iron lungs, and prophylactic anti-retroviral therapy used to treat HIV is less expensive than treating patients for AIDS. Effective therapies for cancers, Alzheimer's disease, and schizophrenia could have similar cost savings in the long run. Where innovation does increase costs in the long run, it is because it creates true health benefits that society values. Given market competition and reimbursement policies tied to value, innovation is thus a key driver of long-term improvement.

The short-term cost implications are more complicated. It is true that new treatments for a disease often command high prices during the exclusivity period before generic manufacturers are allowed to compete.²⁵ These prices reflect a combination of factors—including innovators' need to offset the expense and risk of drug development, their monopoly in selling the drug, and healthcare reimbursement practices that do not always match price to value. This situation would be mitigated to some degree by the availability of multiple competing products, with similar efficacy and safety.

Overall, we believe that the right solution is not less innovation, but more innovation—to increase competition in the short term and expand generic solutions in the long run.

We Stand at a Moment of Historic Progress in Biomedical Research, with Extraordinary Promise for New Drug Development

The past quarter-century has seen stunning progress in basic biomedical research, propelled by powerful research technologies and revealing fundamental information about the basis of disease. The opportunities for biomedical advances have never been brighter.

The tools for biomedical research have become dramatically more powerful. From 1990-2003, the Human Genome Project revealed the human genetic code and also propelled advances that have decreased the cost of sequencing a human genome by roughly one million-fold (from a few billion to a few thousand dollars today). Microarray technologies have made it possible to characterize the

24. Alzheimer's Association. "2012 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia*. 2012. Volume 8, Issue 2; www.alz.org/downloads/Facts_Figures_2012.pdf.

25. See Box on exclusivity periods in Chapter 3.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

responses of cells to perturbations by simultaneously studying the expression levels of all 20,000 human genes. With advances in mass-spectrometers, it is now possible to monitor proteins and metabolites with much greater sensitivity, speed, and completeness than a decade ago. With genetic engineering tools such as germline manipulation and RNA interference, it is now possible to study genes in mice or in human cells by deleting the gene or disrupting its function. With tools to produce pluripotent cells able to differentiate into any cell type in the body, biologists are rapidly learning to reprogram the identities of cells and to compare the effects of different mutations. And, increasingly, researchers are combining tools to measure cellular responses with powerful computational methods to develop ways to reconstruct the “circuits” that drive cellular behavior.

With these technologies, scientists are systematically discovering the genes and proteins that contribute to human diseases. The genes responsible for more than 3,000 single-gene disorders (such as cystic fibrosis or Huntington’s disease) have been identified, and more than 1,500 genes contributing to inherited risk for common polygenic (caused by multiple genes) diseases (such as diabetes and heart disease) have been identified so far. Studies of tumors have also identified more than 300 genes in which acquired mutations contribute to the progress of cancer. These studies will lead to increasingly complete catalogs over the next decade, providing a foundation for understanding the origin and cause of disease.

By combining these powerful tools and information resources with basic biological and clinical studies, researchers have made remarkable progress in understanding the fundamental mechanisms underlying such fields as immunology, neurobiology, development, and cancer.

Some of these discoveries about the genetic and biologic basis of disease have been successfully translated into first-in-class drugs against novel therapeutic targets that are now approved by the FDA and benefiting patients. The identification of specific mutations in cancer has led to therapies targeted against the abnormal proteins. These cases include the drugs imatinib and vemurafenib, targeting genetic abnormalities found in chronic myelogenous leukemia and melanoma, respectively. The discovery that HIV requires the CCR5 protein to infect cells led to the development of an antagonist to this protein, maraviroc, which is now approved for treatment of HIV. And, the discovery of the genetic basis of cystic fibrosis (CF) in 1989 has finally led to the development of a recently approved therapeutic agent ivacaftor (Kalydeco) effective against a specific mutation in the gene carried by 4 percent of patients.²⁶

An estimated 3,000 treatments are in various stages of development, including more than 850 for cancer alone.²⁷

26. Kalydeco was approved on January 31st, 2012. Accessed May 14th, 2012.
www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289633.htm.

27. Munos, B. “Bringing Breakthrough Innovation Back to Drug R&D” White paper for President’s Cancer Panel/NIH from October 2010.

Yet There Are Reasons for Concern About the Pace of Innovative Drug Development

Although biomedical research has experienced a golden age of progress over the past 25 years, there has been growing concern^{28,29} about the pace of translating scientific insight into public health impact. As described above, we still lack effective treatments for most diseases, including the vast majority of cancers and psychiatric diseases. Many high priority public health needs, including the growing burden of neurodegenerative diseases and the emergence of drug-resistant bacterial infections, are not being met with adequate investment and innovation.

As discussed in the next chapter, the remarkable advances in basic biomedical research over the past quarter-century have not yet led to significant increase in the flow of new medicines to the American public. Of course, one should be realistic that the understanding of diseases will not usually translate immediately into powerful treatments: finding molecules with high efficacy and low toxicity is extremely difficult; much progress comes through incremental improvements that ultimately combine to yield large impacts.³⁰

Still, it is concerning that, despite significant increases (in inflation-adjusted terms) in R&D investments by industry, the rate of new drugs entering the market has remained roughly constant for decades. As the time and amortized cost of developing new drugs continues to rise, the large pharmaceutical companies are coming under financial stress and new biotechnology companies are finding that venture capital is becoming scarcer. As a result, innovators seeking to pursue unprecedented approaches to important public health needs face an increasingly challenging environment.

Origin of this Study

In light of these concerns, President Obama asked his President's Council of Advisors on Science and Technology (PCAST) in March 2011 to identify ways to accelerate innovation in the discovery, development, and evaluation of biopharmaceuticals. In response, PCAST engaged in discussions with a wide range of stakeholders—including senior leaders from the biopharmaceutical industry, patient advocacy groups, physician societies, and healthcare payors, and the senior leadership of the FDA and NIH. The process began with informational interviews from April to June 2011, followed by two one-day PCAST subcommittee meetings in summer 2011. From these diverse constituencies, PCAST assembled a group of about 30 invited experts. Informed by extensive discussions with these experts and other knowledgeable parties over six months, PCAST analyzed the situation and developed specific recommendations to the President. This report describes the key issues and recommendations.

28. Pammolli, F., Magazzini, L., and Riccaboni, M. "The productivity crisis in pharmaceutical R&D." *Nat. Rev. Drug Discov.* 2011; 10, 428–438.

29. FitzGerald, GA. "Drugs, industry and academia." *Science.* 2008; 320: 1563.

30. Examples include breast cancer and HIV/AIDS, where physicians took drugs with initially modest effects and ultimately combined them to obtain large therapeutic effects.

Scope of the Report

The scope of this report is limited to PCAST's assigned task of recommending actions that can be taken to propel scientific innovation in drug discovery, development and evaluation. The report does not address many other important policy issues that affect whether therapeutics that are developed will optimally serve the needs of American people. Such issues include drug pricing, reimbursement policy, comparative effectiveness studies, intellectual property, direct-to-consumer advertising, medical education and physician prescribing authority, international trade and competition, and global harmonization of regulation. At the end of the report, we note the need and opportunity for a broader national strategy concerning the therapeutics ecosystem.



II. Innovation Under Stress

The Nation needs continuing innovation in the creation of effective treatments for the wide range of inadequately-treated diseases that affect the public. This innovation depends on a complex ecosystem that involves basic biomedical research in universities and research institutes, clinical research in hospitals, and drug discovery and development in the biopharmaceutical industry. Each of the components of this ecosystem is under challenge.

The budget for the National Institutes of Health increased substantially from 1998 to 2003, doubling in nominal terms.³¹ From 2003-2008, however, the budget failed to keep up with inflation.³² Importantly, the Obama Administration's stimulus package provided a supplemental boost of \$10.4 billion to the NIH budget, spread across several years. But, the prospects ahead are worrying, given the pressures on the Federal budget.

Similarly, clinical research has come under increasing pressure as costs of clinical investigation and clinical trials increase and sources of financial support decline. NIH has recognized the importance of translating basic findings from "bench to bedside" through its CTSA program, but this supports only a small portion of the Nation's clinical research and clinical trials infrastructure.

These challenges need to be addressed by a renewed Federal commitment to the funding of basic and translational research. We make recommendations in Chapter 5.

At the same time, there have been increasing pressures affecting the biopharmaceutical industry. These pressures are important because industrial R&D investment is a critical component of the innovation ecosystem:

- The pharmaceutical industry is facing the largest "patent cliff" in its history: Drugs with annual sales exceeding \$200 billion will come off patent in the period 2010-2014, resulting in a loss of more than \$100 billion in sales to generic substitutions; only a small fraction is expected to be replaced by new product revenues. Decreased prices through generic substitution will benefit the Nation, but will likely also result in decreased resources invested in new areas of R&D.³³ According to some observers, many companies are adopting more conservative approaches to R&D.
- Venture capital to start new biotechnology firms and fund innovative drug development activities appears to be declining, due not only to general economic conditions but to what are cited as concerns about unfavorable returns in the drug-innovation sector. While venture capital funding in all sectors has decreased since 2008, the decrease in number of first-time deals from 2007 to 2009 was significant in the biotechnology (-29.4 percent) and medical/healthcare (-40.0

31. From \$13.7 billion in 1998 to \$27.1 billion in 2003. NIH Budget Office. 2012.

32. Figure from NIH Director's Office in response to request.

33. Paul, S.M., et al. "How to improve R&D productivity: The pharmaceutical industry's grand challenge." *Nature Rev. Drug Discov.* 2010; 9 (3):203-214.

percent) industries.³⁴ Venture capital firms report that they expect to decrease further their investments in the biomedical industry,³⁵ although there is some countervailing data.³⁶ Declining availability of funds for innovative new companies would put increasing pressure on innovation.

- Many companies are exiting important fields of critical public health need. For example, despite the growing healthcare and economic burden of neurodegenerative diseases, such as Alzheimer’s Disease and psychiatric diseases, many major pharmaceutical companies are closing down or severely curtailing drug discovery programs in part because of the rate of candidate failure and the time and cost required to complete clinical trials.³⁷
- The biopharmaceutical industry has not historically been characterized by a large degree of industry-wide collaboration or public-private partnership. However, these pressures have created an environment in which companies appear much more willing than previously to make common cause—to work together and with other sectors—to improve processes for drug discovery, development, and evaluation.

New Drugs: Output Flat, Productivity Declining

Despite dramatic advances in biological knowledge, the rate of new drugs applications and new drug approvals has remained relatively constant for several decades (Figure 1a). (The notable spike of approvals in 1996-97 is widely attributed to the clearing of backlogs, made possible by funds from the newly enacted Prescription Drug User Fee Act (PDUFA) that provided new financial resources to the Agency to support expedited drug review.)

While the output of new drugs has remained constant, total R&D investment by industry in drug discovery and development have grown exponentially, in inflation-adjusted terms (Figure 1a-b). As a result, the amortized R&D cost per newly approved drug has continued to grow. A recent paper estimated that the cost of drug development increased by a factor of two roughly every nine years, and coined this as “Eroom’s law” (in contrast to—and with a backwards spelling of—the well-known Moore’s law concerning the time over which semiconductor costs decrease by a factor of two). We note that precise inferences about the costs of drug development are problematic for many reasons, including that new drugs approved in a given year reflect R&D investments over many prior years; that drugs approved in different time periods may be more or less innovative; and that data about R&D costs may be incomplete or inconsistent. Nevertheless, the broad trends seem clear.

34. Block, J., et al. “Venture capital and the financial crisis: an empirical study across industries and countries.” 2010.

35. A survey of 156 companies conducted by the National Venture Capital Association reported that many firms plan to decrease their investment in the biomedical industry further over the coming 3 years. “Vital Signs: The Crisis in Investment in U.S. Medical Innovation and the Imperative of FDA Reform.” Survey Findings. October 2011. National Venture Capital Association and MedIC.

36. One analysis showed that venture capital financing for biopharmaceutical firms grew in 2011 by 16 percent over 2010, to nearly \$3.5 billion; it is unclear whether this change reflects a reversal of a trend, a shift in investment focus within the biotechnology sector or one-time temporal factors. OnBioVC: 4Q11 & 2011 Trend Analysis. 15 February 2012. Report Code: IDOB 1010. freepdfhosting.com/ef718d6d76.pdf.

37. Abbott, A. “Novartis to shut brain research facility.” *Nature*. 2011.

II. INNOVATION UNDER STRESS

FIGURE 1. (a) Annual NME/NBE Approvals versus R&D Expenditures in 2009 Dollars. (b) Estimates of Cost to Companies per New Molecular Entity in 2009 Dollars.

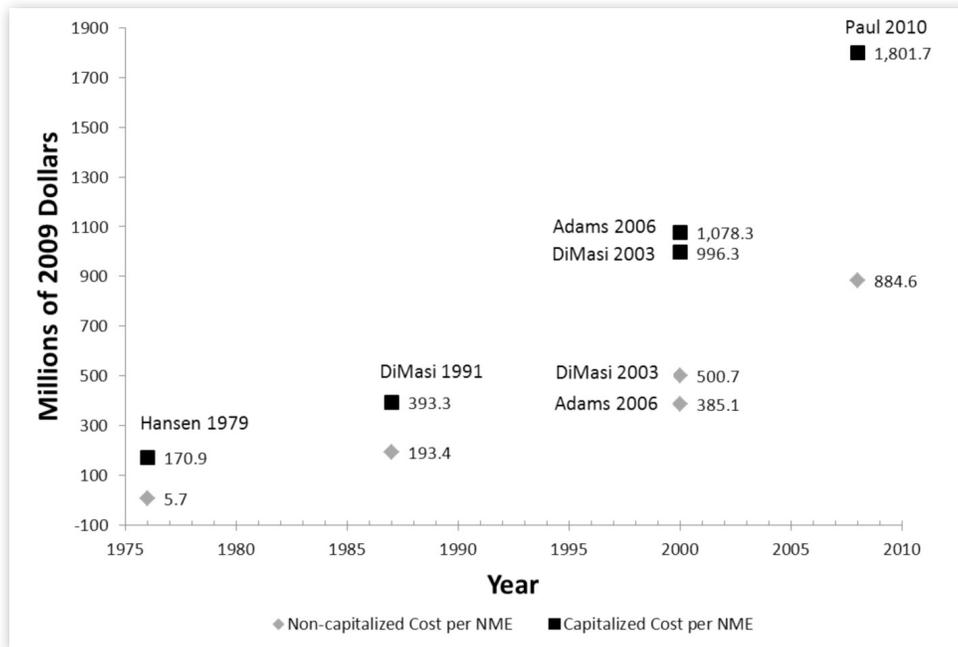
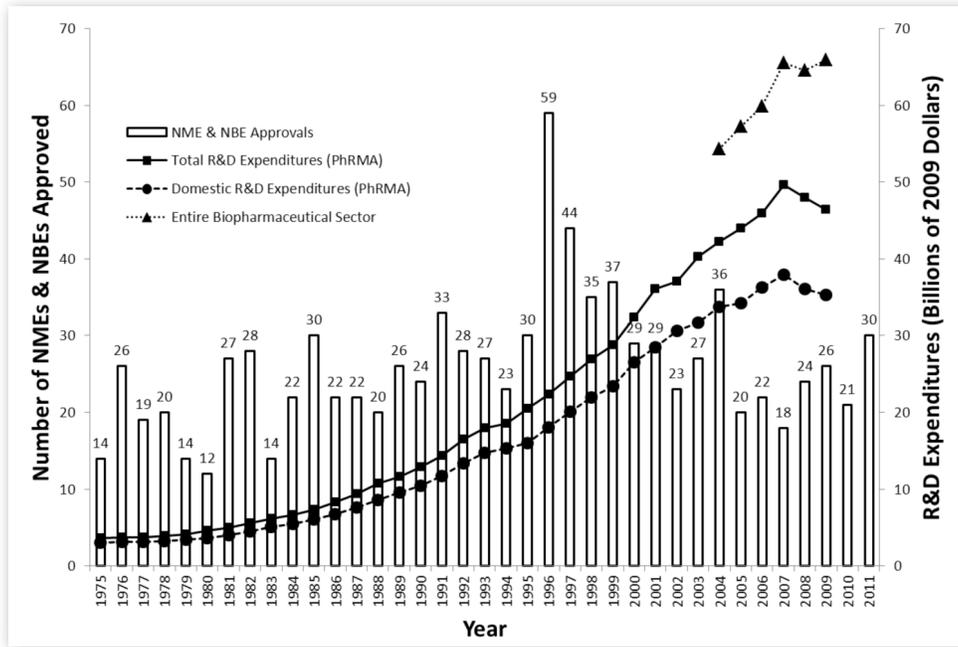


Figure 1. (a) STPI analysis upon PCAST request based on NME and NBE approval data are from the FDA (2012). PhRMA data are from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Member Survey, 2011. Entire biopharmaceutical sector data are from Burrill & Co., analysis for PhRMA, 2006–2011. Both sources are publicly available in the PhRMA 2011 Pharmaceutical Industry Profile. Note: In interpreting the figure, it is important to note that NME/NBE (new molecular entity and new biological entity, respectively) approvals in a given year should not be directly compared with R&D expenditures in that same year because there is a lag of several years between the time of investment and output that can be

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

expected in terms of approved drugs. The estimated time from target discovery to drug approval is 17 years. Nonetheless, falling productivity is evident because costs are increasing at a steady rate higher than inflation but yielding a constant rate of NME/NBEs. The spike in NME/NBE approvals in 1996 is generally attributed to FDA clearing a backlog in submissions due to increased funding from the Prescription Drug User Fee Act, which provided additional resources and imposed time limits on the review of new drug applications. NME/NBE approvals represent the number of NMEs and NBEs approved per year for marketing by the FDA. NME approvals represent small molecule drugs, whereas NBE approvals cover biologics. R&D expenditures include reported expenditures from PhRMA member companies, which are mostly large prescription drug firms with substantial U.S. sales as well as expenditures from the entire biopharmaceutical sector (as reported by PhRMA). Total PhRMA expenditures include both domestic and foreign reported R&D spending, while domestic PhRMA expenditures include spending within the United States by PhRMA member companies. Entire biopharmaceutical sector data include R&D expenditures from PhRMA members, research associates, and non-member companies in the biopharmaceutical sector. R&D expenditures include salaries, materials, supplies, overhead, and the cost of developing quality control as well as R&D funds contracted to outside parties. R&D expenditures exclude capital expenses and routine quality control as well as R&D expenditures for projects conducted through grants or contracts from outside organizations. The White House GDP deflator was used to adjust all cost data to constant 2009 dollars.

(b) STPI analysis upon PCAST request based on Hansen, R.W. "The pharmaceutical development process: estimates of current development costs and times and the effects of regulatory changes" 1979. In: Chien, R.I. (Ed.). "Issues in Pharmaceutical Economics." Lexington Books, Lexington, MA, pp. 151–187. DiMasi, J. A., et al. "Cost of Innovation in the Pharmaceutical Industry." *J Health Econ* 1991; no. 10 (2):107-142. doi: 10.1016/0167-6296(91)90001-4. Adams, C. P., and Brantner, V. V. "Estimating the cost of new drug development: is it really 802 million dollars?" *Health Aff. (Millwood)* 2006; no. 25 (2):420-8. doi: 25/2/420 [pii]10.1377/hlthaff.25.2.420. DiMasi, J. A., et al. "The price of innovation: new estimates of drug development costs." *J. Health Econ.* 2003; no. 22 (2):151-85. doi: S0167-6296(02)00126-1 [pii]10.1016/S0167-6296(02)00126-1. Paul, Steven M., et al. "How to improve R&D productivity: the pharmaceutical industry's grand challenge." *Nat. Rev. Drug Discov.* 2010; no. 9 (3):203-214.

Challenges in Drug Development

Drug development is challenging for a variety of reasons.

- **High probability of failure.** Whether a drug discovery and development project succeeds depends on the answer to key scientific questions, such as: Will a drug that inhibits a target protein be effective against the targeted disease? Will a specific chemical entity be safe? With the current state of knowledge, it is difficult to make accurate predictions and uncertainty is often resolved only late in the development process after the expenditure of considerable time and money. Because the success rate is very low (currently around 9 percent), the true cost of making successful drugs must include amortization of the many failures.

Evidence suggests that the failure rate³⁸ for new drugs in clinical trials is increasing. Between 1993 and 2003, clinical trial failure rates increased from 82 percent to 91 percent.³⁹ At every stage of drug development, attrition rates have been increasing. Success rates in the final stage (Phase 3) of clinical testing—at which point significant investment has already been made in a drug candidate—decreased from 80 percent to 50 percent between 1995 and 2005,⁴⁰ and are now estimated at 45 percent.⁴¹ One analysis showed that half of these Phase 3 drug candidates

38. Failure rate refers to the proportion of drug candidates that enter clinical trials (Phases 1-3) for which sponsors choose not to seek FDA approval.

39. GAO. "Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts." 2006.

40. Woosley, R. L. and Rice, G. "A new system for moving drugs to market." *Issues in Science and Technology.* 2005; no. 21 (2):63-68.

41. Kota, I. and Landis, J. "Can the pharmaceutical industry reduce attrition rates?" *Nat. Rev. Drug Discov.* 2004; Vol 3: 711-715.

II. INNOVATION UNDER STRESS

failed for lack of efficacy,⁴² (even though efficacy should be established in Phase 2) often because the underlying clinical hypothesis about how to treat the disease was incorrect. Another third failed because of safety issues that had not been predicted earlier in development. Increasing failure rates may reflect a greater proportion of drugs with novel mechanisms of action entering clinical trials without adequate proof-of-concept studies in humans.⁴³ (According to some analyses,⁴⁴ drugs with novel mechanisms of action were more than twice as likely to fail as drugs with already-established mechanisms, underscoring the challenges of true innovation.) In addition, some failures are due to insufficient efforts in Phase 2 of clinical trials devoted to optimizing patient selection and dosing.⁴⁵

- **High expenses.** The drug discovery and development process is extremely expensive, with the most expensive factor being the cost of clinical trials. The top 20 companies in the pharmaceutical industry spend about 37 percent of their total R&D budget on clinical trials, approximately \$31 billion dollars annually.⁴⁶ These trials include those that are investigational, before a therapy is licensed for use and the large clinical trials that are often required to investigate the safety of products in the post-marketing setting. (The next largest component is the discovery phase at about 22 percent of costs.) Clinical trials are expensive for at least two reasons: (1) the current clinical trials system is inefficient and (2) current clinical trials often require large numbers of patients and long durations to provide adequate evidence of safety and efficacy to meet the standards for regulatory approval, especially for drugs with clinical impacts which are not dramatic or which occur over a long period of time. Decreasing the cost of clinical trials would directly decrease the cost of drug innovation. There are opportunities to streamline the clinical trials system in the United States in ways that would decrease costs while increasing quality. There are also opportunities to obtain better information about effectiveness from smaller or shorter clinical trials (for example, by using biomarkers to focus on patients most likely to benefit and by using new kinds of trial designs).
- **Long time to market.** The time to market for a drug is a critical factor for innovators, because it affects the amount of time in which a patented product can be marketed before it faces generic competition. Because drugs are very expensive to develop but typically much less expensive to manufacture, an economically rational company will not invest in developing a drug unless there is an 'exclusivity period', during which others are excluded from marketing the same product. (See box on Exclusivity Periods in Chapter 3.) Shorter time to market typically translates to longer exclusivity and greater return. The time to market depends on many factors, including the time taken by the company to develop a drug and the time taken by the FDA to review an application for approval.

42. Gordian, M.A., et al. "Why drugs fall short in late-stage trials." *The McKinsey Quarterly*. 2006.

43. Scannell, J.W., et al. "Diagnosing the decline in pharmaceutical R&D efficiency." *Nat. Rev. Drug Discov.* 2012. 191-200.

44. Ibid.

45. Skarke, C. and FitzGerald, G.A. "Training translators for smart drug discovery." *Sci. Transl. Med.* 2010. 2: 26 cm12.

46. Accenture research performed on behalf of the Hever industry collaboration, a group of R&D heads of pharmaceutical companies. Data provided via personal communication with Garry Neil of Johnson and Johnson.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

Evidence indicates that the time and cost for conducting clinical trials of new drug candidates is rising. Over the past 50 years, the time from drug discovery to drug approval has nearly doubled from 8 years in the 1960s⁴⁷ to roughly 14 or more years now. More recently, some experts conclude that the time required for drug development (from patent filing to commercialization) has increased from an average of 9.7 years for drugs launched during the 1990s to an average of 13.9 years for drugs launched since 2000.⁴⁸ Factors include the increasing complexity of clinical trial protocols, including the procedures to be applied, the growing difficulty of recruiting and retaining patients that meet the criteria for clinical trials, the administrative burdens of setting up clinical trials, and increasing regulatory requirements for clinical trials in particular areas.

- **Regulatory uncertainty.** Drug discovery and development projects also face many uncertainties. Some are unavoidable, as unanticipated issues arise during drug development. Some, however, reflect regulatory uncertainties that might be minimized through clearer and more consistent communications by the FDA. These uncertainties often surround the type and quality of evidence that will be necessary to demonstrate safety and efficacy (for example, for a new drug class, a new indication, or new drug combination). Regulatory risks affect the costs of drug development because investors demand risk premiums to compensate for uncertainty. In this report, we discuss ways to increase regulatory certainty.

While the factors above are important to all innovators, they may be especially important to small biotechnology companies. When the FDA determines that the available evidence is inadequate to support approval and that additional studies are required, a large pharmaceutical firm with many products in its pipeline can accommodate the delay more readily than a small biotech firm. Small firms often have only a single drug under development. Because such companies have no commercial sources of revenue to support their high “burn rate,” a two-year delay in drug approval can be a death knell. The situation illustrates the importance of clear communications with companies, so that they are aware of the requirements they will have to meet to obtain drug approval.⁴⁹

In addition to the economic factors above, some have argued that part of the explanation for declining productivity of the pharmaceutical industry lies in organizational issues and poor execution. Some observers, including former pharmaceutical company CEOs, have asserted that declining productivity is partly due to the size, structure, and management of R&D organizations; too much focus on “blockbuster” and “me-too” drugs; too much attention to sales and marketing;^{50,51} and failure to fully realize the potential of personalized medicine.⁵²

47. DiMasi, J. A., et al. “Cost of Innovation in the Pharmaceutical Industry.” *J. Health Econ.* 1991; no. 10 (2):107-142. doi: 10.1016/0167-6296(91)90001-4.

48. Pammolli, F., Magazzini, L., and Riccaboni, M. “The productivity crisis in pharmaceutical R&D.” *Nat. Rev. Drug Discov.* 2011. no. 10 (6):428-38. doi: nrd3405 [pii]10.1038/nrd3405.

49. In recent years, FDA has made considerable efforts to increase outreach, education, and communication to the small business community. The small business assistance portal provides a wealth of resources, FAQs, and real-time updates (www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm). In addition, each of FDA’s Regional Offices has a small business liaison and the CDER Communications office is available for small business phone or email inquiries.

50. Garnier, J.P. “Rebuilding the R&D Engine in Big Pharma.” *Harv. Bus. Rev.* 2008.

51. Letter from the Editors. “Lessons from Lipitor and the broken blockbuster drug model” *The Lancet.* 2011. Volume 378, Issue 9808, p. 1976. doi:10.1016/S0140-6736(11)61858-8.

52. Aspinall, M.G. and Hamermesh, R.G. “Realizing the promise of personalized medicine.” *Harv Bus Rev.* 2007; 85(10):108-17, 165.

II. INNOVATION UNDER STRESS

Overall, accelerating the flow of innovative medicines will require coordinated action across sectors to address a range of issues, including decreasing the probability of failure, the expense, the time, and the regulatory risk associated with drug development, while maintaining the effectiveness and safety of new medicines.

PCAST believes that there are many opportunities to do so. We propose the following ambitious goal for the Nation:

Goal: Double the current annual output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and government working together to double the efficiency of drug development by decreasing clinical failure, clinical trial costs, time to market, and regulatory uncertainty.

PCAST believes that such a goal is attainable over the next 10-15 years. We also discuss below various intermediate milestones that can be achieved along the way. Achieving this goal will require concerted efforts by stakeholders across multiple sectors—including biopharmaceutical companies, the Federal Government, the research community, and patient advocacy groups of various types. The analysis and recommendations that follow are intended to lay a foundation for such improvements.



III. Improving Drug Discovery and Development

In this chapter, we describe issues related to propelling innovation in drug discovery and development—specifically, knowledge gaps, inefficiencies in clinical trials, and economic incentives.

Gap Between Basic Research and Commercial Projects

The explosion in basic biological knowledge over the past 25 years has not yet given rise to a measurable increase in the rate of new drug development. Some have even gone so far as to argue that the advances in basic research have actually impeded pharmaceutical productivity⁵³ because the availability of thousands of novel drug targets has tempted companies to pursue poorly understood targets. We disagree that this is source of the problem.

The fundamental problem is that advances in basic biomedical knowledge have not yet been matched by similar increases in the science and technologies needed for drug development. Accelerating the translation of biological insights into new medicines requires developing powerful new scientific knowledge, methodology, and tools. Academic scientists tend not to pursue such work, because it is seen as “too applied” and because it often requires multi-disciplinary teams rather than individual academic labs. Companies tend to under-invest in such work because it is at least partially a “public good”—that is, a single company financing the development of new foundational approaches to drug discovery cannot fully appropriate the fruits of the work, because much of it leaks out to benefit all participants.

Two examples illustrate the challenges in drug discovery and development:

- (i) **Predicting efficacy and toxicity.** Developing medicines involves creating molecules to modulate a protein target in the hope of treating a disease. Yet, we currently have only a very limited ability to predict whether (1) modulating a particular target will actually ameliorate a disease in humans or (2) a particular molecule will have toxic side effects. To a large extent, we rely on trial and error. Boeing’s engineers can accurately predict the performance of a new airplane design through computer simulation, because they know the equations that describe air flow. Pharmaceutical scientists, lacking adequate predictive tools, must instead do the equivalent of building the plane to see if it will fly or crash.

A case in point is the recent effort to develop drugs to prevent cardiovascular disease by increasing high-density lipoprotein (HDL). HDL is the so-called “good cholesterol”: in population studies, high levels of HDL are correlated with a decreased risk of cardiovascular disease. Pfizer scientists created an inhibitor (torcetrapib) of a particular enzyme (called CETP) involved in cholesterol metabolism and found that it increased HDL levels and inhibited atherosclerosis in a rabbit model. In Phase 2 clinical trials, the drug increased HDL levels in humans, but also elevated blood pressure.⁵⁴ In a large Phase 3 clinical trial of 15,000 patients, the inhibitor showed significantly

53. Pammolli, F., Magazzini, L., and Riccaboni, M. “The productivity crisis in pharmaceutical R&D.” *Nature Rev. Drug Discov.* 2011. no. 10 (6):428-38. doi: nrd3405[pil]10.1038/nrd3405.

54. Tall, A.R., et al. “The Failure of Torcetrapib.” *Arterioscler. Thromb. Vasc. Biol.* 2007; 27: 257-260.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

increased morbidity and mortality—resulting in a failure that likely cost hundreds of millions of dollars. It is unclear whether the problem was with the fundamental notion of inhibiting CETP (a so-called ‘on-target’ effect) or was a vagary of the specific molecule (a so-called ‘off-target’ effect, in which the molecule inadvertently affects a different cellular pathway). Lacking clear knowledge about the validity of the target, three companies proceeded with clinical trials of alternative CETP inhibitors. Just before this report went to press, one of these companies (Roche) announced that it had terminated its trial for lack of efficacy. In addition, a study showed that individuals who carry genetic variants that exclusively increase HDL levels show no decreased risk of heart attack, which suggests that HDL levels may be correlated with but not play a causal role in protection against heart disease.⁵⁵

Before developing a pharmaceutical, a drug developer would ideally want to: (1) know whether modulating the intended target would have beneficial effect on the disease (“target validation”), (2) know which subsets of patients have a form of the disease that is likely to respond to modulation of the target (patient selection), and (3) have easily-monitored molecular, cellular, or clinical responses that indicate that a candidate drug is actually acting on its target in a patient (biomarkers of response or disease progression). In addition, a drug developer would ideally like to have preclinical tests that would identify candidate drugs that are likely to cause unacceptable side effects (“predictive toxicology”).

Improved knowledge, methods, and tools in these areas would benefit the entire field, by decreasing the risk of expensive late-stage failures. Because the proportion of successful drug development projects is currently around 9 percent, even modest increases in success rates such as back to the historical 14 percent success rate⁵⁶ or higher, would have a significant impact on the amortized cost of drug development. Yet, such foundational work will not be done in the ordinary course of business by commercial teams engaged in specific drug development projects.

As an example, the NIH’s National Center for Advancing Translational Sciences (NCATS), in collaboration with the Defense Advanced Research Projects Agency (DARPA) and the FDA, is exploring an approach for predictive toxicology involving developing a chip carrying various human cell types that can monitor readouts related to drug responses.

The greatest need is for improved methods for target validation. The primary focus should be on early proof-of-concept in humans: drugs based on clear proof-of-concept in humans have much higher success rates than drugs based only on cell or animal models. Human proof-of-concept demonstrations can sometimes be obtained from genetic studies, where naturally occurring genetic variants provide a clear demonstration of the effect of modulating a target. Indeed large-scale genomic studies may greatly expand such information in the coming years. Additionally, clinical investigational studies with small numbers of patients but extensive data gathering can also be extremely valuable in obtaining proof-of-concept.

55. Voight, B.F., Peloso, G.M., et al. “Plasma HDL cholesterol and risk of myocardial infarction: A Mendelian randomisation study.” 2012, *Lancet*, in press.

56. FDA. “Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.” 2004.

(ii) Drugging the “undruggable.” The vast majority of currently approved drugs act against only a few classes of proteins (such as proteases and kinases). Many of the proteins that have been implicated in human diseases belong to classes that are currently said to be “undruggable.” The term suggests that it is impossible to make drugs against such targets, but actually it means only that no one has succeeded to date. Indeed, twenty years ago, kinases were broadly considered to be undruggable. Today, transcription factors and many protein-protein interactions are generally regarded as undruggable.

The ability to create drugs against currently undruggable target classes could dramatically expand the range of possible medicines. Yet, it is not economically feasible to expect companies to take on large research projects to tackle such targets, because success would largely serve to blaze trails for others. On the other hand, it is not practical for most academic laboratories to take on such projects because they lack sufficient expertise, scale, or tools. Moreover, such work runs counter to the usual focus in academic science on testing specific hypotheses.

Recently, the NIH has begun to address the gap between basic research and commercial projects, by focusing on the need for Federal support for research in translational science. In 2011, the NIH proposed the creation of an important new entity, NCATS, to serve as NIH’s catalytic hub for translational innovation. According to NIH Director Francis Collins,⁵⁷ the new center is intended to “catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics, therapeutics, and devices across a wide range of human diseases and conditions.” Importantly, the goal is not to create specific drugs—a task that is better performed in the private sector than in government—but to improve the foundation for drug development. NCATS was established in December 2011. NCATS includes pre-existing programs such as the CTSAs, the Therapeutics for Rare and Neglected Diseases Program (TRND), and components of the Molecular Libraries Program. A new program launched with NCATS includes a collaboration with DARPA to create tissue chips to improve preclinical toxicology testing. Congress also created, within NCATS, the Cures Acceleration Network (CAN) to catalyze the development of high-need cures. CAN has two novel authorities for supporting innovative research: matching grants and flexible research authority. While authorized for up to \$500 million, the CAN appropriation in FY2012 was only \$10M. NCATS is an important development, although it is important to recognize that it will likely be able to address only a fraction of the critical needs.

In addition to NCATS, several specific collaborations and consortia have been formed in the United States, including the Biomarkers Consortium, the Observational Medical Outcomes Partnership, and the Critical Path Institute. The United States-based efforts are valuable, but most tend to be focused on specific topics and projects rather than providing critical mass and leadership. (In Europe, the Innovative Medicines Initiative has a somewhat broader focus.)

The Nation would benefit from a coherent, high-level partnership that brings together high-level leadership from key stakeholders on a sustained basis to develop and help launch initiatives for shared objectives. We discuss this topic in the recommendations in Chapter 5.

57. Collins, F.S. “Reengineering translational science: the time is right.” *Sci. Transl. Med.* 6 July 2011. Vol. 3, Issue 90, p. 90cm17. DOI: 10.1126/scitranslmed.3002747.

Inefficiency in Clinical Trials

Clinical trials constitute the largest single component of the R&D budget of the biopharmaceutical industry, at approximately \$31.3 billion, representing nearly 40 percent of the R&D budget of major companies.⁵⁸ Unfortunately, there is broad agreement that our current clinical trials system is inefficient. One R&D leader of a major pharmaceutical company consulted by PCAST estimated that a more efficient clinical trials system could cut these clinical trials costs by one-third to one-half across the industry.

Currently, each clinical trial to test a new drug candidate is typically organized *de novo*, requiring substantial effort, cost, and time. Drug companies must identify clinical investigators and assemble multi-investigator teams. IRB protocols⁵⁹ must be written and separately submitted to each of many institutions, and approval of these protocols can take several months without necessarily improving the ethics of the research or the protections afforded human subjects. Banking of biological specimens, which can be expensive and complex, is typically tailored to the short-term needs of an individual trial, rather than aimed at the long-term utility of large sample banks with detailed clinical annotation. Information technology is not standardized among trials, impairing the ability to analyze and integrate data. And, trial details, such as the definition of phenotypes, are variable across trials, further complicating the integrated interpretation of multiple studies. Navigating all of these requirements is challenging even for large pharmaceutical companies, and can be daunting for small biotechnology firms. Even in the best cases, the complexities add considerable time to trials—subtracting time from a successful drug’s eventual time on the market without competition.

In response to concerns about costs and delays in public-sector-funded clinical research, the NIH formed the Clinical and Translational Science Awards (CTSAs), which are now a major component of the new National Center for Advancing Translational Sciences. The CTSAs are part of a network of 60 academic medical centers whose mission includes improvement in all processes related to the development, approval, activation, and completion of clinical trials. Some of the innovations being tested have the potential to improve the implementation of clinical trials in all sectors. For example, the CTSAs have developed models for both centralized and reciprocal IRB review, with the aim of shrinking the time from protocol development to patient enrollment. Increasingly, disease-specific networks are being established by NIH institutes, built upon the infrastructure established by the CTSAs.

In some instances, institutions have successfully cooperated to execute a series of clinical trials in an ongoing manner, by creating an enduring infrastructure that facilitates rapid initiation of successive clinical trials with modest additional effort. For example, the TIMI Study Group has led over 50 clinical trials, contributing enormously to the standard of care for patients with coronary artery disease.

Cooperative groups in oncology have led many of the most important clinical trials of new agents, combinations, and treatment regimens. The Multiple Myeloma Research Consortium is a network of

58. Accenture research performed on behalf of the Hever industry collaboration, a group of R&D heads of pharmaceutical companies. Data provided via personal communication with Garry Neil of Johnson and Johnson.

59. Institutional Review Boards (IRBs) are boards at individual institutions, such as academic centers and hospitals, charged with overseeing the compliance of research projects with Federal regulations and the institution’s own policies with respect to research that includes human subjects. IRB protocols are developed by researchers who are using human subjects, and reviewed by the respective boards at each institution. Each IRB will have varying requirements for such protocols and require an independent review process. There are also independent, commercial, and central IRBs that are not unique to each institution.

III. IMPROVING DRUG DISCOVERY AND DEVELOPMENT

approximately 16 leading centers in North America that has opened 37 trials to date, enrolled more than 1100 patients, banked more than 3500 tissue samples, and developed metrics to evaluate its speed—all by leveraging philanthropic resources. Some public-private efforts have also been launched to improve efficiency of clinical trials.⁶⁰

The biopharmaceutical industry would benefit from having enduring clinical trials networks able to perform studies suitable for registration of a new drug, with efficiency and high quality. A series of networks, specific to disease areas, could provide lasting infrastructure for the execution of clinical trials of high quality, with rigorous ethical standards, high-quality data collection, and low per-patient cost. The networks could be operated either as for-profit or non-profit entities. Accredited research sites could be maintained, with feedback and accountability, and able to enroll patients rapidly on new trials. The quality, ethics, and efficiency of clinical trials would be further enhanced through standardization of trial design, IRB review, project management, data collection and processing, and sample banking.⁶¹

Ultimately, the industry, the FDA, and the medical community would need to work collectively to create such trials networks—with initial funding to organize and baseline funding to maintain these networks coming through private sources. But, the long-run return on these investments could be considerable to all contributors.

Beyond organizational inefficiency, clinical trials are also expensive because they often must be extremely large or long to provide sufficient evidence about efficacy. But in fact, it is increasingly possible to obtain clear answers with many fewer patients and with less time. One approach is to focus studies on specific subsets of patients most likely to benefit, identified based on validated biomarkers. In some cases, using appropriate biomarkers can make it possible to dramatically decrease the sample size required to achieve statistical significance—for example, from 1500 to 50 patients.⁶²

Another approach is to use innovative new approaches for trial design that can provide more information more quickly. Bayesian statistical designs potentially allow for smaller trials with patients receiving, on average, better treatments.⁶³ These and other modern statistical designs can improve on current

60. One example is the Clinical Trials Transformation Initiative (CTTI), which is a public-private partnership founded by the FDA and Duke University to identify practices that will increase the quality and efficiency of clinical trials. CTTI now involves more than 60 organizations from across the clinical trial enterprise. CTTI was formed because of the challenges facing the clinical trial system: increasing start-up times, decreasing patient recruitment and enrollment, increasing trial costs, and the shift of many trials from the United States to offshore locations. CTTI has sought to identify both incremental changes (such as standardizing and improving Severe Adverse Event reporting), and transformational changes (such as meta-analysis of the overall system using the Results Database built on www.ClinicalTrials.gov).

61. Since 2009, the Institute of Medicine's Forum on Drug Discovery, Development, and Translation has been engaged in efforts to address challenges facing the U.S. clinical trials enterprise, including through (1) harmonizing regulation and improving infrastructure of clinical trials in the United States, and (2) public engagement in the clinical trials enterprise, including promotion of public understanding of and support for clinical trials and the drug development enterprise. The approaches considered include clinical trial networks that engage and support community practitioners in research. Citation: IOM (Institute of Medicine). "Envisioning a Transformed Clinical Trials Enterprise in the United States: Establishing an Agenda for 2020: Workshop Summary." 2012. Washington, DC: The National Academies Press.

62. The drug imatinib (Gleevec) was approved based on a clinical trial of only 54 patients, because nearly all patients showed marked benefit [<http://www.cancer.gov/newscenter/qa/2001/gleevecqa>]. The drug gefitinib (Iressa) required a clinical trial of approximately 1500 patients because it showed benefit in only a minority of patients. It later became clear that testing the drug in the specific subset of patients carrying mutations in a specific gene (EGFR) would have made it possible to demonstrate efficacy in only about a hundred patients.

63. Berry, D.A. "Bayesian clinical trials." *Nat. Rev. Drug Discov.* 2006; Vol. 5: 27-36.

protocols, which have only a very limited ability to explore multiple factors simultaneously. Such factors importantly include individual patient responses to a drug, the effects of simultaneous multiple treatment interventions, and the diversity of biomarkers and disease sub-types.

Most trials also imperfectly represent and capture the realities of the clinical care setting in which health care is delivered and do not include the full diversity of patients with a disease or the full diversity of treatment results. Integrating clinical trial research into clinical care through innovative trial designs may provide important information about how specific drugs work in specific patients.

Some exciting innovative models for clinical trials have been launched in recent years. (For one example of such efforts, see Box on I-SPY Trials.) However, the barrier to initiating innovative trials remains high, and there is limited ability to scale and disseminate processes and tools needed for such trials. There is a need for improved mechanisms to align parties including drug sponsors, insurers, and the FDA.

In summary, improving the efficiency of clinical trials is an area that is ripe for improvement, but that will require industry and/or public-private consortia to pursue.

I-SPY TRIALS

The I-SPY 1 and I-SPY 2 TRIALS⁶⁴ are examples of pioneering approaches to clinical trials, deployed to create efficiencies in the development of breast cancer therapies by engaging multiple cancer centers across the country, drawing on thorough clinical data, and using innovative trial design. I-SPY 1 involved a collaboration among 10 cancer centers and the National Cancer Institute (NCI SPORE program and the NCI Cooperative groups) to identify the indicators of response to chemotherapy that would best predict the survival of women with high-risk breast cancer. Over the course of four years⁶⁵ (2002-2006), the study monitored 237 breast cancer patients as they underwent chemotherapy in advance of surgery, known as neoadjuvant therapy. The patients' tumors were monitored serially using MRI and tissue samples taken iteratively to determine the biology of responders and non-responders to standard chemotherapy given in a neoadjuvant setting, or pre-surgical setting, across different patients. Evaluating the impact of chemotherapy on the tumor tissue directly was much more rapid than studying outcomes in thousands of patients over long time periods, and helped to standardize the imaging and tumor sampling processes, as well as miniaturization of assays.

Among the key findings of the trial was that tumor response evaluated in this manner was a good predictor of the patients' overall survival, and that tumor shrinkage during the treatment was a good predictor of long-term outcome and response to treatment.⁶⁶ Importantly, the vast majority of tumors were palpable and determined to be high risk by a molecular signature and therefore at risk for recurrence within 5 years. However, there was heterogeneity even within this group of high-risk women and measuring response within tumor subtypes was more informative than measuring response in the group as a whole.⁶⁷ Within

64. I-SPY TRIAL: Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis.

65. In December 2010, the investigators extended the protocol and enrolled 119 additional patients, per www.ispy2.org/about/background-i-spy-1-trial.

66. Esserman, L., et. al. "Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657)" *J. Clin. Oncol.* 2012; in press.

67. Hylton, et al. "MRI Prediction of Response to Neoadjuvant Chemotherapy for Women with Locally-advanced Breast Cancer: Results from the ACRIN 6657/ISPY TRIAL." *Radiology.* 2012; in press.

III. IMPROVING DRUG DISCOVERY AND DEVELOPMENT

genetic signatures, complete pathological response to treatment appears to be a reasonable predictor of good outcome. Additionally, the shared database from I-SPY 1 has furthered the understanding of drug response and generated new targets and agents for subsequent testing.⁶⁸

The findings of I-SPY 1 set the stage for the I-SPY 2 TRIAL, an ongoing adaptive clinical trial of multiple Phase 2 treatment regimens (in combination with standard chemotherapy) in patients with tumors with varying genetic signatures. I-SPY 2 is a collaboration of 19 academic cancer centers, two community centers, the FDA, the NCI, pharmaceutical and biotech companies, patient advocates, and philanthropic partners. The trial is sponsored by the Biomarker Consortium of the Foundation for the NIH (FNIH), and is co-managed by the FNIH and QuantumLeap Healthcare Collaborative. I-SPY 2 was designed to address the growing recognition that different combinations of cancer therapies will likely have varying degrees of success for different subsets of patients, and that conventional clinical trials that evaluate tumor response after surgery require long periods of time and large numbers of patients just to weed out ineffective drug candidates. The goal is to accelerate the pace at which we learn, early in the course of drug development, which drugs will be most effective for which disease subsets.

With traditional clinical trial designs, separate trials would be required to test many different hypotheses. Instead, I-SPY 2 is organized as a standing, ongoing clinical trial process. It can efficiently evaluate different therapy regimes by relying on the predictors developed in I-SPY 1 that help quickly determine whether certain patients with a particular genetic signature in their tumor will respond to a given treatment regime. The trial is adaptive in that the investigators learn as they go, and do not continue to pursue treatments that appear to be ineffective. All patients are screened and subdivided based on tissue and imaging markers collected early and iteratively throughout the trial, so the insights learned about patients from early stages of a trial can inform treatments selected for patients enrolled later.

Treatments that show positive effects on response predictors for a given subset of patients can be ushered to confirmatory clinical trials, while those that are demonstrated to be largely ineffective based on a predictor of patient response can be rapidly sidelined. Importantly, confirmatory trials can serve as a pathway for Accelerated Approval.⁶⁹

I-SPY 2 also creates efficiencies and cost-savings because it can evaluate multiple drug candidates developed by multiple companies, escalating or eliminating drugs based on their promise and ushering in new candidates when drugs are eliminated. By using a single standard arm for comparison for all candidates in the trial, it provides a significant cost-savings over what would be required to evaluate these candidates in individual Phase 3 trials.⁷⁰ All of the data generated are deposited into a database to be shared across the industry.

68. Horiuchi, D., et al, "MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition." *J. Exp. Med.* 2012; 209(4):679-96.

69. Esserman, L.J., et al. "Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657." *Breast Cancer Res. and Treat.* 2011. Esserman, L.J. and Woodcock, J. "Accelerating identification and regulatory approval of investigational cancer drugs." *J. Am. Med. Ass.* 2011. 306(23): 2608-9.

70. More information on I-SPY 2 trials is available on the I-SPY 2 website. Accessed May 14th, 2012. ispy2.org/about/i-spy-2-trial.

Economic Incentives

Because drug development is an expensive and risky process, the potential for economic return is an important factor in attracting innovators and investors. As the cost and time of drug development increases, then (all other things being equal) the potential economic return decreases. For certain areas of drug development important to public health, the economic incentives may become insufficient to elicit adequate investment in innovation.

- One example is the development of new antibiotics to combat the emergence of antibiotic-resistant strains of deadly and debilitating bacterial infections, which is an impending public health crisis. Despite its importance to public health, investment in new antibiotic development is drying up: Just 5 new antibiotics were approved by the FDA from 2003-2007, down from 16 from 1983-1987, and only two new classes of antibiotics have been discovered and developed in the last 40 years compared to twelve classes in the 40 years between 1930-1970.⁷¹ Few major pharmaceutical companies are investing in discovering new antibiotics.⁷² The incentives to invest in new antibiotics against drug resistant bacteria are low for several reasons: (1) antibiotics are often targeted against a subset of bacterial strains so market usage may be limited, trials difficult, and regulatory pathways uncertain; (2) they are often used for short course therapy of one to two weeks (relative to drugs that can be taken for a lifetime like those for chronic diseases); (3) the large number of generics keeps prices low even for innovative drugs; and (4) new antibiotics are often used as a “last resort” which keeps market size small.
- Another example is the development of drugs to prevent Alzheimer’s disease. Alzheimer’s is expected to have a massive toll on our aging population, with some experts predicting that 1 in 85 people globally will be affected with the disease. Because the disease progresses slowly, adequate clinical trials to demonstrate protection in healthy individuals (as opposed to mitigation of symptoms in affected individuals) might require 10-15 years of study in tens of thousands of individuals. Despite the importance to public health, companies would be unlikely to undertake such long studies because they would be unlikely to be able to recover the high development costs in the limited market exclusivity period that would remain. The high failure rate of drug candidates for treating Alzheimer’s in the late stages of clinical testing also contributes to under-investment in this area, because research costs are high and probability of success is low. There is a need for robust predictive markers to enable shorter and more informative trials. Notably, many leading pharmaceutical companies have closed or significantly scaled back their research investments in neurodegenerative diseases (and psychopharmacology, generally) in recent years.⁷³
- Yet another example concerns clinical trials to show the efficacy of marketed drugs for new indications. While there may be strong incentives for sponsors to fund such trials to expand the

71. Singh, M.P. and Greenstein, M. “Antibacterial leads from microbial natural products discovery.” *Curr. Opin. Drug Discov. Devel.* 2000. 3(2):167-76.

72. However, the number of antibiotics in clinical trials has increased significantly over the past three years; the factors involved in this are complex and it is not clear whether this represents a trend or an anomaly.

73. Nutt, D. and Goodwin, G.E. “Summit on the future of CNS drug research in Europe 2011: report prepared for ECNP.” *Neuropsychopharmacol.* 2011; 21, 495-499.

III. IMPROVING DRUG DISCOVERY AND DEVELOPMENT

use of newly-approved drugs in large indications, the incentives are likely to be lower for drugs where the end of the exclusivity period is in sight (for example, within six years) or for smaller indications. In such cases, a sponsor may have insufficient incentive to initiate clinical trials to generate compelling evidence of clinical benefit in additional indications, especially given that physicians are permitted to prescribe the drug off-label based on other evidence. Yet, public health would benefit from the availability of clear evidence from well-controlled trials.

One powerful incentive for drug developers appears to be the length of the exclusivity period, during which the drug is protected from generic competition. Congress has passed various laws aimed at encouraging drug innovation by providing additional exclusivity (or data protection) periods to certain biomedical products, most recently, for new biologics. (See Box on Exclusivity Periods.) Additional exclusivity periods have recently been added for targeted purposes. For example, Title VIII of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, *Generating Antibiotic Incentives Now*,⁷⁴ will provide a number of incentives for antibiotic development including five years of market exclusivity for certain new antibiotics. The exclusivity would be in addition to any other statutory exclusivity that may apply (e.g., new chemical entity, orphan drug), but would run concurrently with any patents for the product.

In addition to exclusivity periods, there is a range of other tools that have been used or proposed to encourage investment, such as advanced market commitments (that guarantee a drug developer access to a particular market), vouchers for priority FDA review of drugs (that can be put toward other drug applications to expedite market access), R&D tax credits targeted at clinical research expenses and orphan drug development,⁷⁵ and insurance guarantees.

The success of the economic tools listed above has been variable and their effectiveness is poorly understood. For example, priority review vouchers have not proven to be very successful incentives for drug sponsors. Economic incentives also affect costs, but the distribution and fairness (across the population and across generations) is not well understood. As we discuss in Chapter 5, the Federal Government should study whether and when extensions of exclusivity periods and other economic incentives would serve the public health.

74. Public Law No. 112-144, 126 Stat. 993 (2012).

75. The Orphan Drug Credit provides a credit of 50 percent of clinical drug testing costs for drugs being tested under section 505(i) of the Federal Food, Drug and Cosmetic Act.

Exclusivity Periods

Federal law provides two main types of exclusivity periods—patent protection and statutory exclusivity,⁷⁶ the latter of which is applied differently in different contexts.

In particular, the Drug Price Competition and Patent Term Restoration Act of 1984 (often cited as the Hatch-Waxman Amendments or Public Law 98-417) provides two types of intellectual property protection to drug developers—partial ‘patent restoration’ and statutory exclusivity (in this case, data protection), which often run in parallel. The Hatch-Waxman Amendments extend the term of certain patents to compensate for a portion of the time the drug spends in clinical development and evaluation. Specifically, the patent life is extended by 50 percent of the development time following the filing of an Investigational New Drug application (IND) plus 100 percent of the time the drug is under review at FDA, up to a maximum of 5 years restored and 14 total years of remaining patent life following FDA approval.

The Hatch-Waxman Amendments also provides statutory exclusivity—a limited period of protection from competition following an FDA approval—for certain drugs. This is a period of time following a new drug approval during which the FDA will not approve certain generic and follow-on applications that rely on the innovators’ data package,⁷⁷ but will accept applications for competing products that do not use the innovators’ data package. For new chemical entities (NCE), this period lasts for five years.⁷⁸ (In principle, generic competitors may conduct their own clinical trials and generate their own data package, but this is rarely done because the high cost is not justified by the benefit of a somewhat earlier entry into the market.)

Special statutory exclusivity provisions exist for orphan drugs and biologics. The Orphan Drug Act protects new drugs intended to treat rare diseases or conditions,⁷⁹ from competition by barring the FDA from approving any molecularly-similar⁸⁰ drug for the same use for seven years.⁸¹

The Biologics Price Competition and Innovation Act (BPCI Act) bars the FDA from approving an application for any highly similar biologic that relies on the data package of the innovator biologic during the 12-year period that runs from the date that the product was first licensed.⁸²

All types of statutory exclusivities, as well as certain patent terms for drug products, can be extended by 6 months if a drug developer fulfills a request from the FDA to conduct clinical trials demonstrating the safety and efficacy of the drug in pediatric populations.

Patent life typically exceeds the statutory exclusivity (or data protection) period, but the validity of patents can be challenged in court by potential competitors. By contrast, statutory exclusivity or data protection periods are not affected by patent challenges.

A key policy issue with all exclusivity periods is balancing the incentive to innovators to produce new medicines or data with potential increased costs to society through delaying the introduction of market competition.

76. In general, statutory exclusivity is actually not protection from all competing products, but rather a period of protection from competitors’ use of innovators’ data packages as the basis for an FDA approval. An important exception, discussed below, is orphan drug exclusivity.

77. For the first four years of this 5-year period, the FDA will not accept applications for generic or other competitor products that rely on the innovators’ data package. In the 5th year the FDA may accept applications accompanied by a certificate of patent invalidity or noninfringement.

78. For new uses or formulations that required clinical trials for approval (but were not NCEs), the period is 3 years.

79. Defined as those with less than 200,000 patients in the United States.

80. Same active moiety.

81. This is the case unless a “parallel pioneer,” a drug sponsor that was developing a nearly identical product for an orphan designation, demonstrates the clinical superiority of its product. (Unlike the exclusivity granted for conventional new chemical entity approvals, the exclusivity provided by FDA for orphan drug approvals extends to slightly different molecules (e.g., an antibody with 2 or 3 different amino acids or an enantiomer). The first drug sponsor to apply for and secure an Orphan Approval receives the 7-year exclusivity that protects its market from all such similar molecules, unless the “parallel pioneer” demonstrates clinical superiority.

82. The FDA will also not *accept* any applications for a biosimilar or interchangeable biologic during the first 4 years of this 12-year period.



IV. Improving Drug Evaluation

Accelerating innovation in the creation of safe and effective medicines will require improvements not only in drug discovery and development, but also in the Nation's regulatory processes for drug evaluation. In this section, we describe the inherent challenges in drug evaluation and the opportunities for improving the system.

We first address a commonly made criticism about the FDA—namely, that the FDA itself constitutes the major barrier to increased innovation in drug discovery and development, because it is inefficient and stodgy compared to its European counterpart, the European Medicines Agency (EMA). In fact, we find that the data for drug approvals do not support this claim. Since the early 1990s, the FDA's review times for new drug applications have declined significantly with the full implementation of the PDUFA. The proportion of applications for new molecular entities that eventually receive FDA approval has remained fairly steady since the 1990s, at about 80 percent.⁸³ When a drug is clearly efficacious, the FDA typically approves it rapidly. The issues that typically attract attention concern cases where the favorability of the balance between benefit and risk is unclear (for example, moderate potential benefit to some patients and large potential risk to other patients).

Importantly, recent studies have shown that the FDA approves drugs faster than the EMA. For 75 percent of new drugs approved by both the EMA and FDA between 2006 and 2010, the FDA was the first to grant approval.^{84,85} Similarly, a recent study found that the FDA approved more new cancer drugs and approved them more quickly than the EMA (on average in 6 months) between 2003-2010, and that patients in the United States consistently had access to those cancer therapies before patients in Europe.⁸⁶ (Because this PCAST study focuses on drugs, we have not evaluated the situation with respect to medical devices.⁸⁷) In short, the FDA remains a respected world leader in drug regulation, setting standards emulated around the globe.

Although this specific criticism above is mistaken, we do believe that there are issues at the FDA that require attention and that there are important opportunities to improve the process of drug evaluation. These opportunities include improving the Agency's tools for balancing risk and benefit; increasing the degree of regulatory clarity in guidance and communications; increasing the scientific and medical expertise available to the Agency in emerging areas, such as pharmacogenomics, biomarker development, or rare disease research; and improving internal management of drug applications.

83. Approval rate is relative to submissions received by FDA. GAO. "New Drug Development: Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development." November 2006, pg. 12.

84. See the FDA transparency initiative website:
www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247470.pdf.

85. An important difference between the EMA and FDA approvals is that products in the United States can be marketed upon receiving FDA approval. In the EU, a committee of the EMA issues a positive opinion to the European Commission, which must adopt the opinion of the EMA before marketing authorization. Some studies, including that cited below, take into account this difference in the review processes when comparing review times, by comparing the dates of effective marketing authorization.

86. Roberts, S.A., et al. "Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe." *Health Aff. (Millwood)*. 2011; No:doi: 10.1377/hlthaff.2011.0231.

87. For a discussion of these issues, see: Kramer, D.B., S. Xu and A.S. Kesselheim. "Regulation of Medical Devices in the United States and European Union." *N. Engl. J. Med.* 2012; 366:848-855.

Improving Tools for Balancing Risk and Benefit

In principle, the FDA should ensure that the American people gain access as rapidly as possible to new drugs that are safe and effective, while ensuring that they are protected as completely as possible from drugs that are not. In practice, it is very difficult to strike this balance because our knowledge about safety and efficacy is often initially very limited and evolves over time. Approving drugs with too little information runs the risk of exposing the public to dangerous side effects or ineffective treatments. Requiring overly large and lengthy studies before approval runs the risk of delaying the availability of efficacious and potentially life-saving treatments. There are thus two ways in which the FDA can fail: by allowing unsafe medical products on the market, or by preventing patients from gaining timely access to innovative and potentially life-saving therapies. FDA must strike a balance between these two competing responsibilities.

The Challenge of Addressing Uncertainty, Risk, and Benefit

The FDA's mission would be challenging under the best of circumstances. But, it is exacerbated by the nature of the typical framework for regulatory approval. Under this framework, the FDA makes a binary decision to approve or reject an application to market a new drug for a specific indication (disease), based on the information available at a specific moment in time. The problems with this framework include the following:

- **The information available about a drug at the time of approval is necessarily incomplete.**

The FDA requires substantial evidence demonstrating the safety and effectiveness of a drug for its intended use. However, even when a product is tested in clinical trials enrolling thousands of people and taking several years, the evidence is still limited. When medical products enter the marketplace, they are often used by millions of patients in populations that differ in important ways from the human subjects who participated in clinical testing. Even if we focus only on patients using the drug for the approved indication, these patients will typically be more diverse along a variety of characteristics including age, genetics, diagnosis, stage of disease, and state of health. Moreover, these patients will use the product in a real-world setting for longer periods of time, where they also take other medications and may have a range of other lifestyle and medical factors that affect the way they respond to a given drug. Clinical trials cannot feasibly predict the full range of rare but serious side effects that might be experienced once a drug is released to a wider population or the variation in effectiveness that might be observed in real-world use. Adverse drug reactions that resulted in drugs being removed from the market have occurred in less than 1 out of 10,000 patients—meaning that to detect them in the clinical trial stage would require enrolling prohibitively large numbers of patients.⁸⁸ This disparity between clinical trials and real-world use of medical products presents a conundrum: knowledge about

88. A randomized controlled trial that includes 7,000 patients in 2 treatment groups (a large phase 3 trial) would have less than 50 percent statistical power to detect an increase of 1 in 500 incidence of an adverse drug reaction that background incidence of 1 in 1000 patients. If that drug reaction were lethal, a drug-induced rate of even 1 in 5,000 might tip the scale against approval. (In 1 million people, it would cost 200 lives.) The trial with 7,000 people could not detect that increase; to detect it with 90 percent confidence would require a trial of 1 million patients. Citation: H.G. Eichler et al. "Balancing Early Market Access to New Drugs with the Need for Benefit-Risk Data: A Mounting Dilemma." *Nat. Rev. Drug Disc.* October 2008, Volume 7: 818-826.

IV. IMPROVING DRUG EVALUATION

a drug's safety and effectiveness is inherently limited at the time of FDA approval, and therefore it is impossible to fully predict its impact on the entire patient population that will use it.

- **Once a drug is approved for one indication, physicians are permitted to prescribe off-label, for indications for which the drug has never been tested or in ways not recommended by the FDA.** Approved drugs can be prescribed off-label by physicians for indications other than what they were tested and approved to treat; by some estimates about 20 percent of prescriptions are off-label.⁸⁹ This medical practice has allowed doctors and researchers to discover new uses of therapies, and to evaluate whether there is scientific evidence to validate such uses. Off-label use has allowed physicians, for example, to learn that beta blockers, originally approved for treating hypertension, are also helpful in treating heart disease.⁹⁰ Off-label prescribing is a widespread practice today by oncologists in cancer treatment, because there is a growing recognition that drugs that block particular cellular pathways may be effective in cancer types beyond those tested in the clinical trial used for approval.

At the same time, off-label use can pose serious risks. When drugs are prescribed by physicians to patients with illnesses that were not evaluated in clinical testing, there may be no evidence about the safety and effectiveness of those drugs in these settings. One study indicated that 73 percent of drugs used off-label lack evidence of clinical efficacy for those uses.⁹¹ There are several drugs, such as gabapentin, that have been found to be prescribed by physicians primarily for off-label uses despite the dearth of scientific support for such uses.^{92,93} In addition to being prescribed for non-approved indications, drugs are frequently prescribed to patients for use beyond the time frame recommended by the FDA or in tandem with other drugs that may cause dangerous interactions—despite labels warning against such use.

While physicians are permitted to prescribe drugs off-label, biopharmaceutical companies are not permitted to promote the use of the drugs for non-approved indications. Yet, there have been a number of instances where companies have been found to have violated this prohibition.

Once a drug is on the market, the economic incentives for sponsors to conduct further clinical trials to obtain formal approval for some additional indications may be low. It may also be challenging to enroll patients in such trials (for example, when a treatment is already in wide use off-label and believed to be effective, patients may not wish to enroll in a trial). Under such circumstances, critical information about the performance of a drug in new indications (or specific patient populations) may never be gathered.

89. Gillick, M.R. *Annals of Internal Medicine*. March 3, 2009 vol 150, no 5, 344-347.

90. Bennett W.M. "Off-label use of approved drugs: therapeutic opportunity and challenge." *J. Am. Soc. Nephrol.* 2004;15:830-1.

91. Radley D.C., S.N. Finkelstein, and R.S. Stafford. "Off-label prescribing among office-based physicians." *Arch. Intern. Med.* 2006; 166:1021-1026.

92. Kesselheim, A.S. et al. "False Claims Act Prosecution Did Not Deter Off-Label Drug Use In The Case of Neurontin." *Health Aff. (Millwood)*. December 2011 vol. 30 no. 12 2318-2327.

93. Steinman M.A., et al. "Narrative review: the promotion of gabapentin: an analysis of internal industry documents." *Ann. Intern. Med.* 2006;145(4):284-93.

- **Although the FDA approves drugs for specific indications, it has a statutory responsibility to weigh the overall benefit-risk balance that will result from its use in the population, including likely off-label use.** Under the Federal Food, Drug, and Cosmetic Act, the FDA has the responsibility, when determining whether to approve a drug, to consider whether the benefits outweigh the risks. The FDA interprets its statutory responsibility to mean that it may deny approval to a drug with a favorable benefit-risk balance in a narrow population if the drug will pose serious risks to a broad population. Drugs have also been removed from the market because they were being used off-label in a way that raised serious concerns. (Examples include Seldane, an antihistamine that caused fatal heart rhythm abnormalities in patients because it was often prescribed—contrary to label warnings—in combination with other drugs with which it interacts, and Bromfenac, an anti-inflammatory that was prescribed for periods beyond the ten-day time frame on its label, resulting in liver failure and death. The FDA requested that both drugs be removed from the market by the companies that sponsored them.)
- **The tools and incentives to monitor the safety and effectiveness of drugs following approval are inadequate.** The inherent uncertainties outlined above underscore the need to generate knowledge about a drug's risks and benefits over time as it is used more widely, in what is known as the "post-marketing phase." A drug might have benefits for diseases beyond the indication for which it was approved by the FDA, for example, or it might have serious risks that outweigh the benefits. The FDA and public health agencies currently lack a robust and systematic way to track and monitor safety and effectiveness for most medical products in the marketplace. According to regulators, this lack has limited their willingness to accept uncertainty about drugs upon approval or rejection. In general, drug use and safety are not actively tracked in the United States, nor is such information routinely and systematically paired with clinical data on patient outcomes and reactions.

The FDA relies in part on a passive surveillance system, known as the Adverse Events Reporting System (AERS). Under this system, patients and health care providers voluntarily report suspected safety issues from a medical product. This requires health care professionals to make a judgment call on whether a particular adverse event is worth reporting as a possible adverse drug effect. It then requires health agencies to separate actual drug-related safety issues from background "noise"—the cacophony of reported issues, many of which are unrelated to the drug. The agencies must then investigate and evaluate safety issues that seem to be significant and related to an approved product in order to justify taking action. In our view, this system is inefficient, inconsistent, resource-intensive, and increasingly obsolete. Recently, the FDA in cooperation with academic researchers and other stakeholders has been developing the Sentinel Initiative, which would allow the FDA to more actively monitor the risks and benefits of medical products in the marketplace. (For further discussion of this issue, see later discussion on Sentinel).

In some cases, the FDA requires drug sponsors as a condition of approval to perform future studies of drugs' risks and benefits in the post-marketing phase (referred to as Phase 4 studies). An Institute of Medicine report in 2007 found that many of these studies have either gone

IV. IMPROVING DRUG EVALUATION

untracked, unfulfilled, or unenforced.⁹⁴ The 2007 FDA Amendments Act (FDAAA) gave the FDA greater authority to compel post-marketing studies under a wider variety of circumstances. Since 2007, there is evidence that compliance, tracking, and enforcement of post-marketing commitments have improved, but it remains to be seen whether the issues have been resolved. The most recent available data from FY 2011 indicate that most post-marketing commitments are completed or are progressing on schedule.⁹⁵

For drugs that have been granted “Accelerated Approval” (explained in more detail later in this chapter), there is evidence of significant challenges in ensuring that sponsors complete confirmatory studies required to verify and describe the clinical benefit of the treatment. A major challenge here is that it can be difficult to recruit a sufficient number of patients to a randomized controlled trial once a drug for a serious or life-threatening disease lacking other effective therapies becomes available to patients.

There is a clear need for improved methods to quickly identify and verify safety issues associated with drugs, and to strengthen incentives to study drugs’ safety and effectiveness in real-world populations. The willingness of the FDA and the public to accept the uncertainty and risks of new drugs—and therefore the ability to support innovation in drug evaluation—is inextricably tied to the quality of information that can be acquired after a drug is on the market.

- **Once a drug is approved, it can be difficult to remove it from the market, even when serious safety issues arise.** By law, the FDA has authority to withdraw a drug’s approval for a specific indication or for all indications. While it occasionally uses that authority, the process is lengthy, cumbersome, and can be challenged in court. In practice, the FDA often asks companies to voluntarily withdraw from the market drugs with serious and known safety issues. Importantly, once a drug is in wide use, it can be difficult in practice to remove it from the market.^{96,97} As a drug becomes prescribed and used by patients, there will inevitably be some patients who believe (often correctly) they are benefitting from the drug and who do not experience negative side effects. If a serious risk of illness or death from a drug is identified and occurs at a high rate in the population, however, the FDA may determine that the risks on balance outweigh the benefits to the public as a whole. Patients and physicians who experience a drug’s benefits and little of its risks may seek to keep the drug on the market by advocating for its approval to remain intact. Moreover, even if the FDA removes approval for one indication for a drug (such as one type of cancer), if it remains approved for other indications (such as other types of cancer), the drug will still be available on the market and physicians may still prescribe it to their patients. The off-label prescriptions of such drugs may be reimbursed by insurers adhering to state laws and to general recommendations of physician societies. (Medicare is required by Federal law to cover off-label uses of cancer drugs listed in one or more approved compendia—reference

94. IOM. *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. Accessed May 15th, 2012. www.nap.edu/catalog/11750.html, pg. 155.

95. Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Requirements and Commitments. Accessed May 14th, 2012. www.gpo.gov/fdsys/pkg/FR-2012-03-06/html/2012-5302.htm.

96. *Ibid* 96, pg. 157.

97. On the other hand, the threat of lawsuits may induce drug companies to take drugs off the market even when FDA would not do so.

books developed by physician, hospital, and pharmacist organizations with information to guide prescription drug use.⁹⁸ In addition, several states require reimbursement of listed cancer drugs by private insurers and Medicaid.)

- **Many believe that FDA approved drugs are guaranteed—or should be guaranteed—to be safe and effective.** Although there is no single moment at which a drug’s full risks and benefits are known, there is a public perception on the part of many that FDA approval signals near-certainty that a drug is safe and effective. In reality, FDA approval signals that risks and benefits have been weighed at a single juncture given a body of evidence that is rigorous but not exhaustive—and the weighing necessarily involves uncertainty about how a broad population of patients will respond and react to a drug.

A recent study of nearly 3,000 American adults found that 39 percent believed that the FDA approves only “extremely effective” drugs, while 25 percent believed that the FDA only approves “drugs without serious side effects.”⁹⁹ Both of these beliefs are mistaken. They also imply that significant portions of the U.S. population likely do not understand that knowledge about a drug’s benefits and risks can substantially evolve—and diverge from what was previously known—after it enters the marketplace and is used more widely.

When severe safety issues do arise with an approved drug, the public and the Congress often blame the FDA for failing to protect the public—whether or not the problem could or should have been foreseen (and such judgments are sometimes hard to make in retrospect). The FDA has been scrutinized and criticized by Congress in high-profile cases over the past decade, including Rezulin, Vioxx, and Avandia. Anticipating such reactions, it is natural to expect that a regulatory agency may choose to proceed cautiously—adopting a precautionary culture, imposing greater requirements for clinical trials, and requiring greater evaluation of drug interactions, liver toxicity, and cardiac toxicity. It is very challenging for the FDA to achieve the optimal balance between maximizing innovation and minimizing risk.

Tools to Address Uncertainty and to Balance Risk and Benefit

In a perfect world, the FDA would have the scientific ability to eliminate risk from medical products, ensuring their complete safety before they reach the marketplace. The reality is that it is not possible to eliminate risk completely, nor to have complete certainty about all the risks and benefits of a drug to a large population.

Nevertheless, it is critical that we strive to expand the evidence base of the FDA and other stakeholders to decrease medical risk, and to improve the degree of knowledge and certainty we have about drug risks and benefits before they are ushered into the marketplace. At the same time, we must continue to balance the time and cost of gaining greater certainty with the urgent needs of many patients for access to innovative treatments.

In order to strike this balance and to accelerate innovation while improving safety, the FDA needs a range of tools that enable it to manage uncertainty and to learn and weigh the risks and benefits of drugs before and after approval.

98. Gillick, M.R. *Ann. of Int. Med.* March 3, 2009 vol 150, no 5, 344-347.

99. Scwhartz, L.M. and S. Woloshin. “Communicating Uncertainties About Prescription Drugs to the Public.” *Arch. Int. Med.* Vol. 17 (16). September 12, 2011: 1463-1468.

IV. IMPROVING DRUG EVALUATION

The tools needed to optimize the approval drugs that have a favorable balance of benefit and risk include:

- Better scientific tools, including predictors of toxicity and benefit to improve regulatory decision-making by increasing the level of certainty about drug risks and benefits;
- Adequate statutory authority and clear interpretation of that authority for early approval of drugs based on indicators, such as disease-specific surrogate and clinical endpoints that have a high likelihood of positive therapeutic response in serious and life-threatening diseases with unmet needs, or early approval of preventatives in especially high-risk patients;
- Robust surveillance systems for collecting post-marketing data about the risks and benefits of medical products, including high-quality and interoperable electronic health records;
- Adequate mechanisms to ensure responsible prescribing by physicians for relevant cases;
- Excellent communications channels to patients and physicians that make clear the risks, benefits, and uncertainty surrounding medical products, as well as the indications and safe methods for use;
- Effective tools to withdraw drugs that have serious safety issues or are not shown to be effective, including reimbursement policies that are responsive to evolving data about safety and effectiveness.

The Federal Government, in partnership with academia and industry, has made progress toward developing such tools. However, further progress is still needed. Below we describe some of the tools and the framework that the FDA currently has at its disposal, as well as their limitations and opportunities for improvement:

- (i) **Accelerated approval.** Accelerated approval is a distinct pathway for FDA approval of drugs that was developed in the early 1990s in response to the HIV/AIDS crisis. Under Accelerated Approval, the FDA has authority to grant an expedited approval to a drug “on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.” It includes the requirement that the sponsor conduct follow-up studies to verify the clinical benefit.

Through this pathway, the FDA can expedite patient access to innovative drugs for serious diseases with unmet needs. In doing so, it approves drugs based on their effect on likely predictors of clinical outcome (rather than on clinical outcome itself), known as surrogate endpoints, or on clinical endpoints other than survival or irreversible morbidity. (For a discussion of risks and benefits associated with the use of surrogate endpoints, see the box below.) The advent of this pathway has allowed for the development of pioneering and life-saving HIV/AIDS and cancer drugs over the past two decades.¹⁰⁰

100. For example, protease inhibitors and non-nucleoside reverse transcriptase inhibitors approved in 1996 combined with already approved AZT led to new combination therapies for HIV which greatly decreased AIDS mortality to the point that it became a chronic disease rather than a death sentence. Source: McGee, *P. Drug Discovery & Development magazine*. Vol. 9, No. 7, July, 2006, pp. 10-16.

Surrogate Endpoints and Intermediate Clinical Endpoints

Under certain circumstances, the FDA will approve a drug based on its demonstrated impact on an endpoint that is likely to predict the desired clinical outcome. These endpoints are known as “surrogate endpoints.” Surrogate endpoints are used as the basis for an FDA approval in two types of circumstances:

(1) If a surrogate endpoint is considered to be *validated*¹⁰¹ by the scientific community as having a high likelihood to predict the desired clinical outcome. Examples include reduction in blood pressure, which is viewed as a predictor of decreased risk of stroke, and reduction in LDL cholesterol, which is viewed as a predictor of decreased risk of heart attack and increased survival. In these cases, the FDA has approved drugs, such as blood pressure drugs and statins, on the basis of these surrogate endpoints under its traditional approval pathway. The FDA considers very few surrogate endpoints to be validated, and thus few of them are used as the basis of approvals.

(2) If a surrogate endpoint is determined to be *reasonably likely to predict the desired clinical outcome and the drug that demonstrates an impact on the surrogate endpoint is for a serious or life-threatening disease for which there is unmet need*. Importantly, in this circumstance, the surrogates are considered non-validated, and are associated with greater uncertainty. An important historical example was the reduction of HIV viral load as a likely predictor of increased survival in AIDS patients. A current example is a significant increase in the period before a tumor of a given cancer type continues to grow (progression-free survival) as a likely predictor of increased overall survival (see accompanying box). In these cases, the use of a surrogate endpoint is used as the basis for an Accelerated Approval because of the serious nature of the disease and lack of good treatments for patients. The FDA requires confirmatory studies after the initial approval to demonstrate that the drug not only affects the surrogate but has efficacy on the desired clinical outcome (thus providing evidence supporting the use of the surrogate as a predictor of the clinical outcome), in the case of HIV viral load, the surrogate endpoint was subsequently supported through clinical trials demonstrating direct impact on clinical outcomes.

Surrogate endpoints provide a way to approve drugs without first having to prove the long-term impact on the clinical outcome. In the case of non-validated surrogate endpoints, the use may be justified when the disease is serious or life-threatening and patients lack alternatives. Greater use of surrogate endpoints for these types of diseases and patients could play an important role in encouraging the development of therapies and getting them to patients quickly via the Accelerated Approval pathway, as it did with HIV/AIDS.

However, there is a risk that the use of non-validated surrogate endpoints may not accurately predict the clinical benefit of a drug or that smaller trials may not adequately characterize a drug’s risks. As with all traditionally-designed or Accelerated Approval trials, there is a risk that off-target toxicities may offset the benefit of a drug. This can happen for a variety of reasons.¹⁰² Examples include the drug torcetrapib,

101. For an endpoint to be deemed as validated by FDA, it is typically necessary to show that it predicts the desired clinical benefit across multiple drug, and possibly multiple drug classes. Once a surrogate endpoint is validated, the FDA will accept it as the basis of traditional/full approval. Unvalidated surrogate endpoints can be used in appropriate cases for Accelerated Approval, as described above.

102. Reasons for the failure of a surrogate to adequately predict may include that the surrogate is not in the causal pathway of the disease process, that the drug only affects one causal pathway of the disease (related to the surrogate), and that the drug acts on the surrogate in a manner independent of the disease process. Source: Fleming, T.R., and DeMets, D.L. “Surrogate End Points in Clinical Trials: Are We Being Misled?” *Ann. Intern. Med.* 1996; 125:605-613.

IV. IMPROVING DRUG EVALUATION

a CETP inhibitor intended to increase HDL levels, mentioned earlier in this report, and the drug mibefradil, which lowered blood pressure and reduced angina pectoris but was associated with serious, life-threatening abnormalities of heart rhythm. Rosiglitazone and muraglitazar, diabetes drugs that acted on the surrogate hemoglobin A1C, may cause the serious side effect of heart attacks in their patients. Vytorin, a drug that lowered LDL as a surrogate for heart disease, later appeared to not have a significant impact on atherosclerosis. These examples are compelling reasons why surrogate endpoints should be used cautiously for diseases that are not life-threatening. It is critical that the scientific community engage in ongoing efforts to validate surrogate endpoints proposed for use or currently in use.¹⁰³

In addition to surrogate endpoints, the FDA may also use intermediate clinical endpoints as a predictor of overall clinical benefit. The difference between an intermediate clinical endpoint and a surrogate endpoint is that the former is in of itself a measure of how a patient feels, functions, and survives, while the latter is typically a laboratory measure or test (such as a scan or blood test). Examples of intermediate clinical endpoints could include using the speed at which a patient can walk for a length of time as a predictor of a heart disease patient's functional improvement or using improvements in minimal cognitive impairment as a likely predictor of delayed progression of Alzheimer's disease. The FDA currently tends not to use intermediate clinical endpoints in Accelerated Approvals. However, there are opportunities to expand the use of intermediate clinical endpoints in the case of serious or life-threatening diseases that have unmet needs, as the basis for Accelerated Approvals.

It is important to note that, when relying on surrogate endpoints and intermediate clinical endpoints, the FDA cannot be certain about a drug's efficacy on the long-term clinical outcome. As a result, efforts to expand the use of such predictors of clinical outcome must be complemented by greater rigor in enforcing and fulfilling confirmatory studies that demonstrate the actual efficacy of drugs on clinical outcome. Through such studies and greater monitoring of drugs in the marketplace (including through observational data and electronic health records), the FDA might have greater ability to gain certainty about a product's benefits and risks after approval.

103

103. It is also important to understand off-target effects, as they may eventually lead to other uses for a drug or other knowledge helpful to the understanding of drug and disease types.

Example of a Surrogate Endpoint: Progression-Free Survival

Surrogate endpoints are often used in the evaluation of cancer drugs, with progression-free survival (PFS) commonly serving as a surrogate for overall survival (OS). PFS and OS refer to lengths of time following administration of a drug, with PFS being the time until the tumor resumes its growth and OS the time until the patient dies.

Using PFS as a surrogate endpoint allows both shorter and smaller clinical trials to establish a likelihood of efficacy. The trials can be shorter because tumor progression is an earlier event than patient death. The trials can be smaller because PFS typically has less variance than OS, which requires a larger sample size to reach the same level of statistical significance.

A simple example illustrates the point. In the absence of treatment, suppose that a particular cancer has average PFS of 6 months and average post-PFS survival (that is, OS minus PFS) of 18 months, with both times being exponentially distributed. Suppose that a drug increases PFS by 3 months with no further effect on post-PFS survival, thus increasing OS by 3 months. A two-armed clinical trial (designed to have 90 percent power) would require 400 patients to prove the PFS benefit, but 1800 patients to prove the OS benefit. With an enrollment of 30 patients per month, a PFS trial would require 19 months while an OS trial would require 75 months.¹⁰⁴

An important issue for regulators approving drugs on the basis of PFS is to ensure that post-marketing clinical studies are performed to confirm the treatment's effect on PFS, to validate a favorable risk-benefit balance for OS and to study side effects in larger populations.

Drugs with PFS benefit will typically also confer OS benefit, except if the drug actually shortens the post-PFS survival period. (Such rebound effects have rarely been documented, but OS benefits are sometimes not seen due to insufficient sample size.) In general, PFS has generally proven to be a good predictor of OS and has guided the continuing clinical development of cancer drugs and treatment regimens.

Accelerated Approval is intended to signal to the public that there is uncertainty about the benefit-risk profile associated with a drug, but that, based on predictors of long-term clinical benefit, the serious nature of the disease, and the lack of good alternatives for patients justify early access for patients coupled to a requirement for ongoing knowledge-generation. (It is important to note, however, that the public does not always understand the standard for Accelerated Approval and may believe that Accelerated Approvals have greater certainty or evidence associated with them.)

By statute, the FDA can use Accelerated Approval for any drug that meets an unmet medical need for a serious and life threatening illness.¹⁰⁵ In principle, many drugs and diseases might qualify for the pathway. In practice, however, the use of the Accelerated Approval pathway has been largely limited to HIV/AIDS and cancer drugs.¹⁰⁶

104. Calculation provided by J. Reimann and J. Helterbrand, Geneetech, personal communication.

105. 21 U.S.C. 314.500 Subpart H; 601.42, Subpart E.

106. GAO. "FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints." GAO-09-866, Oct 26, 2009. At the time of the writing of that GAO report, 79 out of 90 Accelerated Approvals were for HIV/AIDS, cancer, or inhalation anthrax. However, in some cases, Accelerated Approval has been used for non-cancer and HIV/AIDS conditions, such as the following examples: Makena for pre-term birth, Letairis and Remodulin for pulmonary hypertension, Exjade for chronic iron overload, Xyrem for cataplexy and narcolepsy, Synercid for resistant bacterial infections, Thalomid for leprosy, drugs for hereditary angioedema and Factor XIII deficiency, and influenza vaccines.

IV. IMPROVING DRUG EVALUATION

The law also allows the FDA to use (as the basis of approval) the standard that a drug “upon a determination that the product has an effect on a *clinical endpoint* or on a surrogate endpoint that is reasonably likely to predict clinical benefit.”¹⁰⁷ [Emphasis added.] An example of an intermediate clinical endpoint is how fast a patient can walk in a given amount of time, as a marker functional improvement in a patient with congestive heart disease.¹⁰⁸ However, the use of intermediate clinical endpoints for Accelerated Approval has been limited (11 approvals in 20 years). Increasing the use of intermediate clinical endpoints could speed the development of drugs for serious diseases.

A GAO report in 2009 concluded that industry fulfillment and agency enforcement of post-marketing studies required as a condition for Accelerated Approval has been inadequate in some cases,¹⁰⁹ and that some surrogate endpoints have not been sufficiently confirmed to correspond to clinical benefit.¹¹⁰ Strengthening the ability to study drug safety and benefits in the marketplace is critical if Accelerated Approval is to be used more broadly.

Without the need for new legislation, the FDA could expand its use of Accelerated Approval to address more types of serious diseases with unmet medical need and to use intermediate clinical endpoints. The agency would also need to signal to industry that this path for approval could be used for more types of drugs, and to specify what kinds of candidates and diseases would qualify. The agency would also need to be confident in the fulfillment of post-marketing studies and the validation of surrogate and intermediate clinical endpoints.¹¹¹ This will require a robust exercise of FDA’s existing authorities and, possibly, additional authorities.

(ii) Managing risks associated with marketed products. When the FDA approves a new drug, it should ideally have tools to manage risks associated with the product. The issues include known and unknown risks associated with the approved indication, as well as with off-label uses.¹¹²

Under the FDA Amendments Act (FDAAA 2007), FDA has the authority to require drug companies to develop and implement risk evaluation and mitigation strategies (known as REMS) in order to manage a known, serious risk with a given product that could otherwise not be made available to patients. REMS aim to monitor and control distribution and labeling of products through various mechanisms, such as including detailed medication guides on how products should be used, and physician registries requiring providers to track their patients or perform

107. 21 U.S.C. § 356(a)3.

108. Clinical endpoints are measures of how a patient feels, functions, or survive and are the ideal dependent variable affected by a drug or treatment in clinical trials. Surrogate endpoints are laboratory measures that are distant but predicted to be related to a clinical endpoint (e.g. tumor size reduction as a surrogate endpoint for patient survival), and are sometimes acceptable bases for approval under the Accelerated Approval pathway at FDA. Intermediate clinical endpoints are those that are also related to how a patient feels and functions (e.g. less difficulty breathing), but are not the ideal endpoint that the drug intends to affect (e.g. asthma).

109. Avorn, J. “Paying for drug approvals—who’s using whom?” *N. Eng. J. Med.* 2007; 356: 1697-1700.

110. GAO. “New Drug Approval: FDA Needs to Enhance its Oversight of Drugs Approved on the Basis of Surrogate Endpoints.” September 2009.

111. FDA has indicated a need to do this in cooperation with physicians’ societies and patient organizations.

112. We note that some off-label prescribing, particularly in oncology, has allowed physicians to help develop evidence-based indications for drugs. On the other hand, there are serious risks with off-label prescribing. See earlier discussion of this issue.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

certain screening tests before prescribing. REMS proposals by the drug sponsor (either made independently or in consultation with the FDA) must be reviewed and approved by the FDA.

Under the REMS framework, the FDA does not directly interact with physicians or patients but rather requires a company to take actions. The REMS mechanism is invoked in response to a known safety issue concerning a drug about to enter, or already in, the marketplace. The FDA believes that REMS is not an effective framework for strongly signaling when a new medicine should be limited to certain subgroups of patients.¹¹³ Moreover, the FDA's use of REMS has generally been limited to when a specific, known safety issue arises.¹¹⁴ The FDA generally does not consider REMS an effective tool to address uncertainty about risks and benefits to the broad population.¹¹⁵

This limitation is illustrated by the case of a drug with a favorable benefit-risk balance in patients with a severe manifestation of a disease (for example, morbid obesity) but an unfavorable or uncertain benefit-risk balance in patients with a mild manifestation (for example, mild obesity). Ideally, the FDA would approve the drug for patients with morbid obesity while taking steps to minimize the likelihood that the drug is prescribed widely to mildly obese patients, which include about 78 million American adults or 35 percent of American adults.¹¹⁶ However, the FDA does not believe that REMS are an adequate tool to allow it to approve drugs for use in the narrow population by discouraging prescription in the broader population. (Another situation would be approval of a drug to prevent a disease for use in a subpopulation at especially high risk, e.g., a genetic predisposition to diabetes.)

One approach could be for the FDA to implement a mechanism under which sponsors could choose to seek approval of a new drug under a new designation: Special Medical Use (SMU). The sponsor would (1) propose a development process to address the benefit-risk balance in a specific subpopulation at high risk from the disease, using the same standards for efficacy and safety as for the existing approval pathways (traditional or accelerated) and (2) demonstrate that clinical trials in the larger population of patients would require much longer to complete or would not be feasible. If sponsors decide to complete broader studies, they could broaden their market and approved indication by submitting additional evidence to the FDA. The initial

113. According to the FDA, restricted distribution requires a central pharmacy with special shipment to restrict access, or onerous pharmacy-based verification systems. To restrict distribution broadly across the country for a widely used drug would be cumbersome, FDA officials say, as even existing REMS have proven to be difficult for the health care community.

114. Some industry observers believe that the FDA has used REMS for uncertain and wider risks to broad population, but the FDA maintains that this has generally not been the case. Regardless, it is clear that REMS does not constitute an adequate tool to strongly signal prescribers and payors how certain drugs ought to be prescribed.

115. According to the FDA and legal experts, the statute neither explicitly prohibits nor explicitly enables the FDA to use REMS as a way to limit the use of a drug to a defined population when the risks to the broader population are uncertain. FDA officials point to the need for a specific framework for drug approval that would effectively restrict initial approvals to specific subpopulations, to be enforced by reimbursement policy of health care payors.

116. About 6 percent of adults in the United States are severely (or morbidly) obese (with a Body Mass Index of 40 or higher), while about 35 percent of adults are obese (with a Body Mass Index of 30 or higher), according to the most recent available data from the CDC's National Center for Health Statistics, via the National Health and Nutrition Examination Survey (NHANES) 2009-2010. Source: www.cdc.gov/nchs/data/factsheets/factsheet_obesity.htm.

designation, however, would give them an early foothold in a market for a narrow population or indication.

The purpose of a new pathway and designation would be to signal to physicians and insurers that, based on current evidence, the FDA considers the drug to be inappropriate for use outside the specific subpopulation. While not forbidding off-label use by physicians, the designation would, in practice, need to strongly influence decisions by physicians and formularies, reimbursement decisions by health care payors, and malpractice insurers.¹¹⁷ If so, the new designation could decrease (although not eliminate) the likelihood of off-label use and thereby enable the FDA to grant approval consistent with ensuring an overall benefit-risk balance. Following initial approval under a new designation, sponsors could apply for subsequent approval without the special designation by conducting clinical studies that address the risk-benefit balance in broader patient populations.

Some observers contend that the FDA has adequate authority to create a new designation already. However, some at the FDA believe that its authority is unclear and that the SMU designation would carry greater weight if explicitly authorized through legislation. We discuss this topic in the recommendations in Chapter 5.

(iii) A tool for post-marketing surveillance: Sentinel. The 2007 FDA Amendments Act (FDAA) mandated a rigorous, active surveillance system, known as the Sentinel System, to track and monitor the safety and effectiveness of drugs in the marketplace. Efforts to launch this system for post-marketing surveillance, known as FDA's Sentinel Initiative, are currently underway. (The current system for post-marketing surveillance via adverse event reporting is described in previous sections of this chapter.)

A pilot for Sentinel, known as Mini-Sentinel, was launched by FDA in 2009 and is being coordinated by researchers at Harvard Pilgrim Healthcare Institute to develop the methods for using multiple databases to identify and analyze post-market medical product safety. Mini-Sentinel has the capacity to examine healthcare data, with strict patient privacy and security safeguards, with the aim of detecting important signals related to safety and effectiveness of medical products. The pilot is working to develop approaches to identify potential safety signals and methods to determine whether safety signals indicate adverse events associated with medical products.

The Sentinel Initiative currently involves insurance claims data from about 125 million patients, as well as electronic health records for about 10 million patients.¹¹⁸ It is increasingly incorporating more electronic health records as they become available. The system can already query databases to analyze adverse events that are recorded in insurance claims, such as allergic reactions, heart attacks, liver failure, stroke, and hip fractures to try to determine whether they are associated with drugs, and investigates further using information from clinical notes and lab data. Sentinel has the potential to become more robust as more electronic health records

117. We note that some past efforts, such as the use of "black box" warnings on high-risk medications, have been less effective than hoped for because they are often ignored by physicians and patients. It will be important to learn from such experiences.

118. Platt, R. et al. "The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction." *Pharmacoepidemiol Drug Saf.* 2012; Volume 21, Issue Supplement S1, pages 1–8.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

become available and searchable by the system, given that they could provide more detailed information on clinical care important for linking (or delinking) risky side effects or benefits with drugs taken by patients. In coming years, post-marketing surveillance may also draw on real-time sensor devices that are increasingly being used by consumers. The data from such devices may provide extremely rich information about safety, adverse events, drug reactions, and drug effectiveness and may help identify correlations of events with patient characteristics.

Sentinel has been funded via the FDA's internal allocation of resources to date, and lacks a line-item appropriation to ensure its ongoing viability and the crucial steps of scaling it up to cover a broader population and drawing upon robust electronic health record systems.¹¹⁹ Current funding is based on available overall appropriations to FDA and has varied over the life of the program from about \$12 million to \$26 million.¹²⁰

Expanding Sentinel and creating a sustained funding source could allow it to be a robust system for monitoring drug safety, which would support the FDA in weighing risk and benefit at the time of approval in support of innovation. In our view, consistent funding of at least \$40 million per year is needed to support the maintenance and enhancement of a robust medical product surveillance system based on current operating costs of the data coordinating center and scaling up the incorporation of data from electronic health records.

In addition to Sentinel, the Observational Medical Outcomes Partnership (OMOP) was an effort aimed at developing methodologies for a medical product monitoring system. It was led by the Foundation for the National Institutes of Health, as a public-private partnership funded by the pharmaceutical industry to test and develop the research methods for querying databases to understand drug-related adverse events. Through various approaches, including the use of simulated data, OMOP has tested the viability of methods for detecting known associations between drugs and safety issues and to refine those methods for use by researchers. (As noted earlier in this chapter, it is difficult to determine what is signal and what is noise in such data without prior hypotheses, and this will be an ongoing challenge as more data are opened up for use in Sentinel.) OMOP is expected to become part of the Reagan-Udall Foundation (RUF), and to continue development of methodologies for post-market studies of drug risks and benefits under the Foundation's guidance. Development of methodologies for post-market studies may also be undertaken by the Patient-Centered Outcomes Research Institute (PCORI).

(iv) Incentives for ongoing study (expanded clinical trials): Pediatric Exclusivity Example. The Food and Drug Administration Safety and Innovation Act (FDASIA, Section 501) permanently reauthorizes the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, in which Congress gave the FDA authority to encourage companies to study adult drugs in

119. The PDUFA fee collections have in the past, and likely will continue to provide funding for the FDA to fulfill some aspects of drug safety activities required by the FDA Amendments Act of 2007 (FDAAA). In PDUFA IV/FDAAA, additional fee amounts were added to generally support post-market drug safety work. Under PDUFA V/FDASIA, some fee funds are specifically directed to an initiative involving Sentinel. In addition, the generic drug user fee (GDUFA) and biosimilar biological product user fee (BsUFA) programs, newly authorized under FDASIA, will provide additional resources that can augment funding for FDA post-market drug safety.

120. Source: FDA interviews, January-April 2012. In addition to this funding, Sentinel received about \$9 million in one-time funds dedicated to medical countermeasures. Two centers at FDA, CDER and CBER, have also allocated between \$1.7 million and \$4.7 million per year each to support specific studies of queries or development of capabilities specific to the medical products they regulate.

development or already in the market to see whether they are safe and effective for children. This has resulted in a wealth of useful information for administering drugs in children including information on dosing, safety, and efficacy. The provision provides six months of additional market exclusivity (attached to the end of a patent term) to an already-approved drug if a company conducts expanded clinical trials in pediatric populations in response to a written request from the FDA. Before the pediatric exclusivity provision was passed, few drugs were studied for their effectiveness and safety in children, despite the fact that children's physiology is clearly different from adults.¹²¹ As a result of the new pediatric studies, new formulations, dosing recommendations, and information about risks and benefits for children became available for these drugs.¹²²

Limitation: The pediatric exclusivity provision demonstrates the ability to incent companies to generate additional information about marketed drugs in return for an economic benefit. However, the provision applies only to studies of already approved drugs for the use in children. The FDA lacks a mechanism to incentivize more broadly studies of drugs already on the market. Some observers have also noted issues with the pediatric exclusivity provision. Not surprisingly, some studies indicate that companies tend to focus on those drugs based on their profitability in the adult market rather than the public health importance of studying them in children.¹²³ In addition, there is evidence that some of the pediatric studies have been of low quality or lacking proper peer review by medical journals.¹²⁴

Opportunity: Legislative provisions to provide incentives to companies to conduct important clinical trials could help ensure the generation of information about risks and benefits of marketed drugs, and thus might help the FDA manage uncertainty upon approval. Provisions that add exclusivity to the end of the patent term and that have the potential to expand the market for a product appear to have a measure of success in encouraging further study.

Enhancing Regulatory Certainty for the BioPharmaceutical Industry as a Whole

In any regulated industry, innovators benefit enormously from clarity about what new innovations will be acceptable to regulators. In particular, innovative drug developers need to understand the regulatory pathways for new products and the regulatory standards for clinical evidence that will be acceptable to the FDA in approving new drug applications. Uncertainty or lack of understanding of FDA policies and practices creates business risk, which can discourage investment and innovation. Ultimately, this impacts the public's ability to benefit from innovative medicines. The FDA should thus have effective procedures to determine its standards in new areas and to communicate its policies and practices.

121. Kesselheim, A.S. "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation. *N. Engl. J. Med.* 363;19. November 4, 2010; 1855-1862.

122. Rodriguez W., et al. "Improving pediatric dosing through pediatric initiatives: what we have learned." *Pediatrics* 2008; 121:530-9.

123. Kesselheim, A.S. "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation. *N. Engl. J. Med.* 363;19. November 4, 2010; 1855-1862.

124. Benjamin Jr., D.K., et al. "Peer-reviewed publication of clinical trials completed for pediatric exclusivity." *J. Am. Med. Ass.* 2006; 296:1266-73.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

It is a commonly stated concern that the biomedical industry lacks adequate certainty about FDA policies and standards, and that this affects their ability to invest in innovative therapies.¹²⁵ We recognize that there are challenging issues regarding new and rapidly emerging opportunities and technologies. Providing rapid guidance is important, but also clearly challenging. In recent years, there has been uncertainty about a variety of important new or emerging issues:

- Appropriate studies for combination therapies, which are increasingly important in cancer and infectious disease such as tuberculosis, where single agents may have modest or no efficacy but combinations may be much more effective.
- The regulatory pathway for therapies for which patients are selected based on a companion diagnostic. Increasingly, therapies are appropriate and effective only in patients with particular molecular markers identified by a diagnostic tool. (The companion diagnostic might or might not be approved already adding a layer of regulatory complexity for the sponsor.)
- The endpoints that constitute an adequate basis for approval. A good example is the circumstances under which the FDA will approve a cancer drug based on delaying tumor progression (progression-free survival or PFS) or will require demonstrating an increase in overall survival (OS). PFS usually—but not always—translates to OS, but proving OS will typically require a much longer and larger trial. (See box on PFS earlier in this chapter.)

In addition, companies may wish to incorporate innovative tools into clinical trials, such as specific biomarkers to identify subsets of patients. Before using new tools, companies need assurance that the FDA will consider the tools to be reliable and consistent enough to support regulatory review. The industry thus seeks clear, up-to-date information about what tools are suitable for use in their development programs and about FDA's standards for demonstrating the validity of tools.

Good guidance and policy to set standards in such areas must be based on strong science. It is important, however, that the policies adapt to emerging knowledge and science by tapping into the broader scientific community.

Guidances

The FDA produces guidance documents that communicate standards to the external community. Guidance documents represent the Agency's current thinking on a topic related to drug development or regulatory science.¹²⁶ The documents are closely monitored by industry as a signal of what is required and expected of them in nearly every aspect of drug development from IND to full-scale manufacturing. They also encourage predictable, consistent decisions by FDA during the regulatory process. Guidances typically arise when a need is identified by senior FDA staff, is pointed out by external groups such as patient advocates or industry, or stems from a commitment outlined in the PDUFA. Indication-specific guidances seek to delineate a clear development pathway so that drug developers know what steps to take to support an efficacy claim for a particular indication. They also provide advice on the human

125. GAO. "New Drug Development: Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development." November 2006; pg 31.

126. FDA guidance can be found on the FDA website. Accessed May 14th, 2012.
www.fda.gov/RegulatoryInformation/Guidances/default.htm.

IV. IMPROVING DRUG EVALUATION

safety studies needed to support the claim. Other clinical guidances may provide general policy or methodological advice. (For example on trial design issues or the uses of pharmacogenomics tests.) Most guidances are issued first in draft form to solicit feedback, with the intent to ultimately produce a final version.

Producing and finalizing guidance documents in a timely fashion is challenging. FDA staff members must study a rapidly evolving field at the forefront of science or medical practice, anticipate the potential issues, and then chart an acceptable regulatory course. The FDA maintains a list of guidances it is currently working on, to keep stakeholders apprised of its activity.¹²⁷ The relevant FDA staff members often have many competing demands on their time. The documents must then undergo significant review by various other staff and offices at the Agency. The most important guidances, from the perspective of the external community, often experience the longest delays because of the scientific and regulatory complexity they pose. Others face delays in the transition from draft stage to final document, where the feedback provided from the broader biomedical community is being taken into account. For example, the FDA's draft guidance on companion diagnostics took about six years to complete, and the adaptive trial design draft guidance took about three years.¹²⁸ Many other important guidance documents are still in process or have not been updated for many years. Examples include guidances that have yet to be drafted, finalized, or updated for: use of multiple endpoints in clinical trials, use of enriched trial designs, Good Review Management Practices, REMS, and non-inferiority trials.¹²⁹ The flow of innovation requires that regulatory pathways for new areas be clarified more rapidly. It is also critical that guidance documents be systematically reviewed and updated in light of changing technology or medical practice innovations.

Some guidance documents are felt by many to provide insufficient clarity. A commonly cited example is the recent draft guidance on adaptive clinical trials. The guidance defines two types of adaptive trial designs—"well understood" and "less well-understood." Observers say that designs that hold the greatest potential for innovation are largely relegated to the "less well-understood" category, and it remains unclear whether this designation means unacceptable or acceptable to FDA. In addition, some observers believe the FDA should have consulted more with the biomedical community in writing the guidance, before issuing its draft. As a result, innovators may be discouraged about pursuing such types of designs.

The FDA could streamline and prioritize its processes for generating guidance documents, although limitations on staff numbers and expertise will constrain its ability to produce guidances as rapidly as needed. In addition, the FDA could use more informal mechanisms to clarify language in already-issued guidance and in describing changes to policies and practices.

To speed the process, the external community could take a more active role in generating input to the FDA on critical topics. If a wide set of stakeholders and experts (including companies, patient groups,

127. This Guidance Agenda is maintained on the FDA website. Accessed May 14th, 2012. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647.pdf.

128. FDA interviews. December 2011. Additional discussion of the guidance process was described and reported by GenomeWeb. Accessed on May 17, 2012. www.genomeweb.com/dxpgx/companion-dx-guidance-nearing-release-fdas-mansfield-offers-some-provisional-adv.

129. As of January 2012, 178 of 559 total FDA guidances were still in draft form, and 100 were 15 years or older. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079645.pdf.

physicians, and researchers) can agree on an approach, it is likely to provide a good starting point for the FDA in preparing guidance. The FDA can then focus its resources to critically review the input.

Qualification of Drug Development Tools

The FDA also provides clarity to the industry through Qualification Statements (appended to guidance documents) stating that a particular tool has been validated for use in clinical trials. These tools include biomarkers that help identify patients who are likely to benefit from a given treatment. The FDA published a guidance document in October 2010 describing the steps that companies should pursue to qualify tools. Since then, there have been at least 20 toolsets proposed for qualification by the biomedical community.

The FDA acknowledges that the Agency has been relatively slow in advising on, reviewing, and issuing qualifying letters for drug development tools, owing to insufficient staff resources. It may be possible to engage the external community to assist in this effort in a transparent and reliable way. For example, the community could help develop recommendations for the conceptual framework and scientific standards that should be applied to the qualification process. The community might also engage in demonstration qualification projects that use the framework and standards. For example, physician societies might convene members via a workshop, or conduct literature reviews and physician surveys to gather data on possible new endpoints and then attempt to validate these endpoints. In addition, there may need to be greater integration of FDA centers in the effort, including officials who determine both device and drug policy.

Enhancing Regulatory Certainty for Individual Drug Development Plans

In addition to clarity about general regulatory pathways and acceptable tools, drug sponsors benefit from clear and frequent communications with the FDA about their specific projects from the earliest stages through final review (See Figure 2). Clear and consistent answers are important because they help companies avoid costly mistakes in designing a project. Rapid answers are important because they avoid expensive delays; this is particularly important for small companies, which often have a single product in development, a high burn rate and limited capital. There are many challenges in optimizing the communication between drug sponsors and the FDA.

Figure 2: Overview of the Drug Development Process and NDA Review Process.

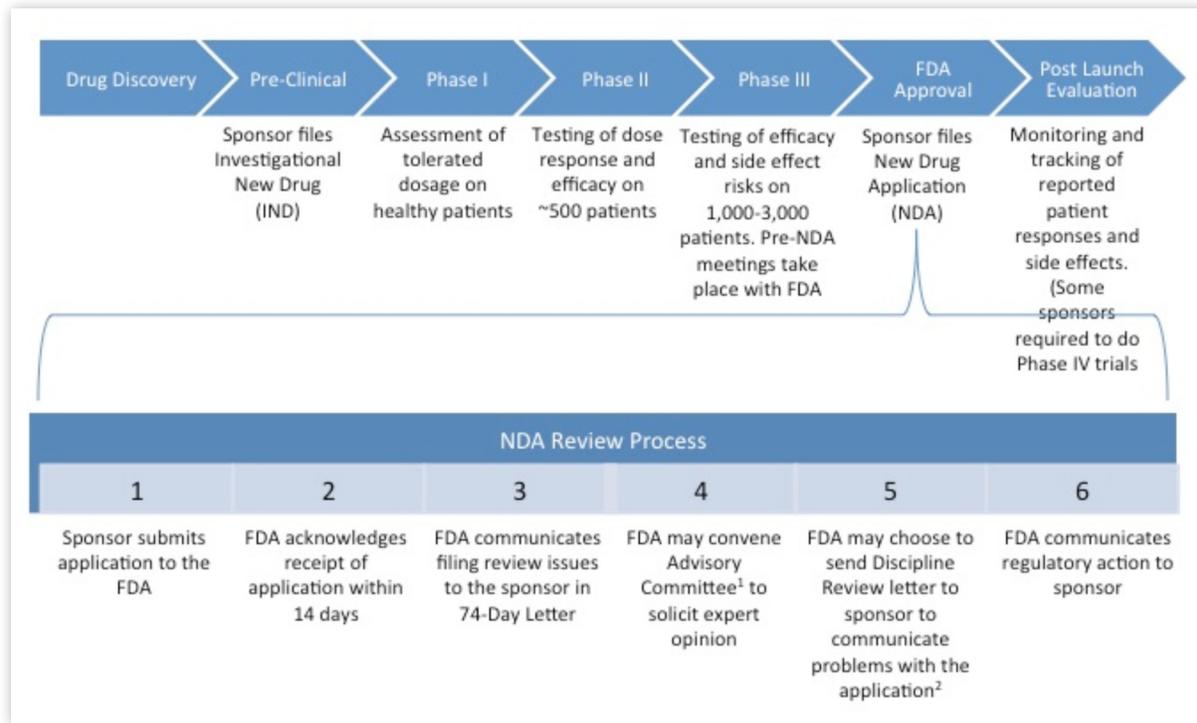


Figure 2. STPI adaptation upon PCAST request. Figure adapted from a similar figure in the California Healthcare Institute’s *Competitiveness and Regulation: The FDA and the Future of America’s Biomedical Industry*, 2011, California Healthcare Institute and Boston Consulting Group, p. 22. The process was initially described in the FDA document *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*, 2005, FDA. ¹Particularly for applications where the drug is the first member in class, if clinical studies involve novel clinical or surrogate endpoints, or if application raises significant safety, efficacy, or public health issues. ²This step does not necessarily temporally follow meeting of the Advisory Committee.

Problems in Communications Between FDA and Sponsor

The Prescription Drug User Fee Act (PDUFA), enacted in 1992, is a system by which the biopharmaceutical industry pays fees to the FDA to cover the costs of drug evaluation and the Agency agrees to performance goals in reviewing drug approval applications. PDUFA imposes many requirements, and deadlines on the FDA. In FY 2011, for example, these requirements directly led to more than 15,000 PDUFA-related goals, meetings, and reports. These PDUFA requirements are meant to ensure that the FDA formally responds within a defined time period to certain formal requests and submissions from sponsors.¹³⁰ While PDUFA is widely applauded for having expedited drug review times, it has raised significant issues. Some observers have expressed concern that it creates dependence on the part of the Agency on the pharmaceutical industry, in part because the user fees now comprise a large pro-

130. Examples include pre-investigational new drug application (pre-IND) meetings (21 CFR 312.82), certain end-of-phase 1 meetings (21 CFR 312.82), end-of-phase 2 and pre-phase 3 meetings (21 CFR 312.47), pre-new drug application/biologics license application meetings (21 CFR 312.47), dispute resolution meetings (21 CFR 10.75, 312.48, and 314.103), and meetings for Special Protocol Assessments.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

portion of the FDA budget for drug evaluation. Some observers also report that the communications process under PDUFA is often stilted. The FDA's need to keep up with the formal PDUFA requirements has limited its ability to provide the sort of rapid and informal communication that can be very helpful to drug sponsors in formulating and adjusting plans. Moreover, the FDA's perspective on a development program may evolve over time; it is essential that sponsors know of such changes. (These issues are being addressed to some extent under the 2012 reauthorization of PDUFA through additional resources and commitments).

Sponsors need a clear, consistent, and timely understanding of FDA concerns about their drug development plan, yet they often express frustration that this understanding can be difficult to obtain for two reasons. First, FDA staff is stretched thin addressing formal PDUFA milestones due to insufficient total funding from Federal appropriations and PDUFA. Second, the review process for each drug lacks a single high-level individual tasked with responsibility for providing clear, consistent ongoing advice to the sponsor. As a drug progresses from the pre-investigational stage (pre-IND) to final consideration for approval (NDA), many staff across divisions and offices are involved in the review. There are also significant imbalances in workload across divisions, which have a variable and unpredictable impact on clinical review holds, review timelines, and ultimately total time to approval.^{131,132} In summary, no single individual has authority and accountability for integrating the input, resolving conflicting opinions within the FDA, and communicating informally in a timely ongoing manner. The lack of clarity and continuity often leads to a perception by sponsors that "FDA is moving the goal posts."

One solution would be for the FDA to designate, for each drug development project, a senior staff member to serve as "pre-market review leader." This individual would be a "quarterback" for the drug development project, with responsibility for providing sponsors with substantive, informal, clear, and timely advice, and for coordinating and leading FDA responses across diverse areas, including toxicology, trial design, manufacturing and clinical use, and for ensuring that timely decisions are made to resolve outstanding FDA review issues. Pre-market review leaders would be valuable for all sponsors, and could be especially helpful for small companies bringing their first product through a regulatory approval. Such a system could greatly improve regulatory certainty, timeliness of FDA decisions, and encourage innovators and investment in innovation.¹³³

131. Milne, C-P, and Kaitin, K.I. "FDA Review Divisions: Performance Levels and the Impact on Drug Sponsors." *Nat. Clin. Pharmacol. and Therap.* March 2012; Vol. 91(3).

132. For example, in a first review of the implementation of Good Review Management Practices (GRMPs) of division data from 2005–2007, only one of the offices examined had a compliance rate of more than 50 percent with GRMPs. None of the other offices achieved more than 25 percent compliance.

133. The additional review time and emphasis on communication in the recently signed FDASIA may address some concerns.

Legal Barriers to Communicating Information

The FDA often faces another challenge in fully and transparently communicating the basis for its decisions or requests, because it believes it is not legally permitted to share information or concerns with a given sponsor that arise from the review of applications and protocols submitted by other sponsors.¹³⁴ This constraint contributes to a sense that advice, decisions, or standards upheld by FDA are arbitrary, rather than informed by confidential data that only the FDA has the benefit of seeing.

Issues with Special Protocol Assessments

FDA has mechanisms to provide much greater certainty to drug sponsors, such as the Special Protocol Assessment (SPA) agreement. Established in 1997 by the Food and Drug Modernization Act (FDAMA) and the renewal of the Prescription Drug User Fee Act, SPAs involve a binding, written agreement between a sponsor and the FDA that a particular outcome in a defined Phase 3 clinical trial protocol will suffice for approval. SPAs provide a high degree of certainty to a sponsor, reducing concerns that the Agency will change its judgment about the evidence required for approval after a trial has been begun or completed.

Sponsors have the right to request a SPA for many Phase 3 trials.¹³⁵ The use of SPAs grew consistently until the past few years, when annual requests for SPAs have dropped.¹³⁶⁻¹³⁷ Under PDUFA, FDA aims to respond to requests for SPAs within 45 days and it meets this target more than 80 percent of the time. However, the overall SPA negotiation process may be lengthy, involving many cycles of interactions extending over long periods. As a result, many drug sponsors say that they choose not to pursue SPAs. In addition, while precise data are lacking, anecdotal evidence suggests that some divisions within the FDA tend to discourage SPAs and that the existence and quality of the subsequent review process (type A meetings) varies greatly across divisions.¹³⁸ In addition, SPAs are not generally used with adaptive trial

134. The FDA and others cite a number of statutes and regulations that restrict the Agency's ability to disclose a sponsor's confidential commercial information or trade secrets, which include much of the information contained in investigational new drug (IND) applications and new drug applications (NDA). During the development process, the FDA is prohibited to disclose to the public or other sponsors confidential commercial information or trade secrets, per 21 CFR 20.61. (FDA regulations on this point implement laws including the Federal Trade Secrets Act (18 U.S.C. 1905), which prohibits the publishing or disclosure of trade secrets and the Freedom of Information Act, which protects from public disclosure trade secrets. Section 301 (j) of the Federal Food Drug and Cosmetic Act (22 U.S.C 331(j)) also prohibits the sharing of commercial information deemed trade secrets.) FDA regulations 21. C.F.R. 312.130 and 314.430 further stipulate what information can be disclosed to the public from INDs and approved/unapproved /abbreviated NDAs. These include the FDA's prohibition on discussing or disclosing the specifics of a pending application, and restrictions on disclosing the existence of a pending application until after approval (unless the drug sponsor has publicly disclosed it.) The FDA also believes that using information from one sponsor's application to inform another sponsor of potential problems could be considered a "regulatory taking," under the Fifth Amendment, which prohibits taking property for public use without adequate compensation. Sponsors have an investment-backed expectation that their data on safety and efficacy (and other information) will be held in confidence by the FDA, and thus could have an argument against the FDA's sharing of that data or information given how the courts have interpreted the property rights of drug sponsors.

135. The law limits SPAs to the clinical trials that will constitute the primary demonstration of effectiveness for the drug. There are other requirements such as the need for an end of phase 2 meeting, or equivalent before an SPA is filed with FDA for review. In addition to Phase 3 trials, SPAs can also be used for carcinogenicity testing and final product stability.

136. Carter, L. and Schumaker, C. "Best practices for special protocol assessment." *Drug Inf. J.* 2008; no. 42 (1):9-12.

137. PDUFA Annual Performance Reports, FY 1998-2010. Accessed May 15th, 2012.

www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm.

138. Osborne, R. "The special treatment." *Nat. Biotechnol.* 2008; no. 26 (5):487-489.

designs.¹³⁹ (See Chapter 3.) Yet these trials are the most challenging to design and would ideally involve a great deal of collaboration and agreement between FDA and the sponsor.¹⁴⁰

Management Issues at FDA

In addition to the issues above, general management and infrastructural issues at the FDA pose challenges for the Agency in achieving its mission. These issues affect all aspects of drug evaluation, from providing efficient responses to drug sponsors to providing clarity on standards and pathways for innovative products to deploying tools to balance benefit and risk such as surveillance systems. These issues include:

Inadequate IT Systems to Support Efficient Management and Communication

Although the FDA is fundamentally an information agency, its information technology systems are woefully inadequate and lacking in key analytical and coordination capabilities. (A report in 2007 by the FDA Science Board addressed some of these issues in depth.¹⁴¹) The agency receives an increasing number of drug applications in electronic form, but it still receives a significant number on paper. Additionally, the data are not standardized, making it difficult and time-consuming to validate and put into a form suitable for analysis and to perform complex analyses. The FDA has no ability to integrate, manage, and analyze data from those applications across offices and divisions.

Many of the IT systems across centers and divisions are incompatible and outdated. As a result, each new drug submission may involve significant manual data manipulation and use of several kinds of IT systems. The system also impedes timely communications with sponsors. The FDA has historically had a series of *ad hoc* efforts aimed at improving the IT systems, but they have not had the planning and critical mass to solve the problem. The FDA's recent hiring of a new Chief Information Officer (CIO) with experience from the pharmaceutical industry holds the promise of developing a coherent and streamlined system, but financial and personnel resources are severely lacking to modernize, update, and integrate systems for efficient delivery, receipt, and analysis of information about new medical products. Without modern IT capabilities and systems and fully electronic submission with standardized data, the FDA cannot adequately support innovation in the biomedical industry; this crucial function underlies all aspects of management, communication, and process.

139. As outlined in the FDA draft guidance on Adaptive Design Clinical Trials for Drugs and Biologics. Accessed May 15th, 2012.

www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. The FDA guidance states "Special protocol assessments (SPA) entail timelines (45-day responses) and commitments that may not be best suited for adaptive design studies" and "FDA cannot realistically commit to accepting aspects of study design yet to be determined. Thus, although an adaptive design SPA request that had been preceded by adequate advance discussion, enabling a complete protocol review, the FDA response may have certain limitations that an SPA regarding a non-adaptive study would not require.

140. FDA indicated in their draft guidance on adaptive trial designs that the 45-day limit on agency's review of SPAs makes the agreements inappropriate for adaptive trial design. However with end-of-Phase 2 meetings and sufficient consultation SPAs could indeed be quite helpful in providing certainty and predictability in the high-risk, high-unknown design of adaptive trials.

141. FDA. "FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology," November 2007. Accessed May 15th, 2012. www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf.

Beyond simply bringing the FDA's IT infrastructure up to modern standards, the FDA should more broadly plan for a world in which electronic data plays a much larger role in health care. This includes both wider use of electronic health records by physicians, as well as use by consumers of personal devices that continuously monitor aspects of health. In principle, such information can enable more effective and more rapid observational studies of the benefits and risks of drugs. Machine learning techniques can be used to identify patterns in clinical data and post-marketing surveillance that identify potential issues much more quickly and with finer granularity than current approaches. Such information could lead identification of specific patient subsets that respond differently to a drug or to algorithms for adjusting drug usage.

To accomplish these goals, the FDA will need to fundamentally rethink its information architecture. Many of the key issues were outlined in PCAST's report "Realizing the Full Potential of Health Information Technology [HIT] to Improve Healthcare for Americans: The Path Forward" in December 2010. Briefly, PCAST observed that communication among all parties using HIT would be greatly facilitated by standardized metadata tags. The FDA should consider how to incorporate this approach into its next-generation IT system—emphasizing metadata, provenance, privacy controls, and well-maintained indices that span all information repositories.

Access to Scientific Expertise

In order to effectively support biomedical innovation in its decisions about specific products and more broadly in its policies, the FDA needs to be guided by the most up-to-date and robust scientific knowledge. Although the FDA has many in-house scientific experts, it suffers from talent recruitment and retention problems including high turnover, inflexibility in organizing its workforce, and lack of time and resources for its scientists to engage with the external scientific community. According to some observers, scientific expertise is inconsistent across review divisions, in particular with respect to review of safety data. This leads to greater regulatory uncertainty and disparity with respect to outcomes of drug reviews.

Moreover, the FDA faces the fundamental challenge that in any given area of expertise, most experts work for someone other than the Agency. Although the Agency draws on external experts for making decisions about particular products through the use of advisory committees, the use of outside experts is constrained by law, by regulatory policy, and by culture and practice. Some of these constraints are necessary; for example, it is important to prevent people who have financial gain at stake (i.e. direct conflicts-of-interest) from guiding decisions about specific medical products. Yet it is important to balance those concerns with the crucial need for consultation with the scientific community, particularly in complex or niche areas.¹⁴² Many important FDA advisory committee slots go unfilled in critical areas each year due to what are deemed conflicts-of-interest, undermining the opportunity for the Agency to draw on leading scientific expertise in those realms,¹⁴³ and often external experts are not available for certain

142. For instance, in the area of orphan diseases, there may be only a handful of experts in the world knowledgeable about a specific disease and all experts may be involved as investigators in the pivotal clinical trials because of the small population size of the orphan disease. A true disease expert is needed to inform the rest of an advisory panel and, in principle, it should be possible to protect the integrity of the decision-making process by fully and publically disclosing the participation of the rare disease expert.

143. Reports showed that in 2010, between 25-32 percent of advisory committee slots (from 49 committees in total) were vacant at the centers for drugs, biologics, and devices at various points during the year.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

meetings. Waivers permitted by law and FDA policy allow some individuals with conflicts-of-interest to serve on advisory committees each year, but the number of waivers FDA provides consistently falls below the allowable annual quota. An FDA study of past advisory committee membership indicated that members who received waivers to serve despite an established conflict-of-interest were significantly more qualified for those committees than the members who had not received such waivers.¹⁴⁴ In April 2010, the FDA Commissioner issued draft guidance to agency staff to promote more consistency in the use of such waivers. This was an important first step. Further efforts are needed to ensure consistent high-quality expertise within the Agency.

Mechanisms to Assess Management Needs, Pilot Reforms, and Ensure Consistency and Accountability

Generally, there is a need for greater understanding of what initiatives and reforms at FDA could improve management and communication during the drug review process—and to ensure that those initiatives are consistently and optimally applied across the Agency. Currently, FDA leadership lacks mechanisms to evaluate management issues and improve the consistency of processes. The agency also requires greater flexibility to test new ways of improving the management of the review process, and to identify the best approaches and scale up and ensure their consistent implementation. A program for piloting management reforms and initiatives and learning from their outcomes could help the FDA address this.

The FDA also needs structures and mechanisms to evaluate the consistency of management practices across the Agency and to ensure accountability. Many observers cite inconsistent scientific expertise across review divisions, especially with respect to review of safety data, as a serious issue. This inconsistency leads to greater regulatory uncertainty and disparity with respect to outcomes of drug reviews.

Including Encouraging Innovation within the FDA's Mission Statement

To ensure a steady stream of new safe and effective medicines for unmet medical needs, the FDA must balance two roles: (1) encouraging innovation in discovery and development to promote public health while (2) serving as a gatekeeper to keep unsafe and ineffective medicines from the marketplace. The FDA's mission statement as defined by law recognizes the second role, but currently does not explicitly acknowledge the role of encouraging innovation in drug discovery, development, and post-marketing evidence-generation. It could be valuable for the Congress to establish that encouraging innovation in drug development is a clear component of the FDA mission.

144. Eastern Research Group. "Financial Conflict-of-Interest Disclosure and Voting Patterns at FDA Advisory Committee Meetings." Report to the FDA Office of Policy, Planning, and Preparedness. January 15, 2009. Accessed May 15th, 2012. www.fda.gov/downloads/AdvisoryCommittees/AboutAdvisoryCommittees/UCM165328.pdf.



V. A Path Forward

Recommendations for Propelling Innovation in Drug Discovery, Development, and Evaluation

We stand at a moment of extraordinary promise for biomedicine, propelled by scientific and technological advances over the past several decades that have resulted from wise public investment. Yet there is widespread concern that scientific discoveries are not being translated rapidly enough into urgently needed medicines for patients. The output of new therapies relative to investment of the biopharmaceutical industry has been falling steadily for several decades, amidst a perfect storm of factors: increasing failure rates, increasing clinical trial costs, increasing time to market, increasing risk aversion, and increasing uncertainty concerning regulatory paths for innovative drugs.

We propose the following ambitious goal:

Goal: Double the output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia, and government working together to decrease clinical failure, clinical trial costs, time to market, and regulatory uncertainty.

PCAST believes that achieving this goal is possible over the next 10-15 years.¹⁴⁵ As described below, various intermediate milestones toward the overall goal can be achieved more rapidly. Achieving the overall goal will require advances in: the science of drug development; the execution of clinical trials; the development pathways used for innovative medicines; the mechanisms for drug approval, surveillance and communication of risk; and management at the FDA. These improvements will unleash extraordinary innovation and investment in the service of public health. Achieving this goal will require active involvement and collaboration among stakeholders across multiple sectors.

Below, we make recommendations concerning specific public and private actions to accelerate innovation.

A. Improving Drug Discovery and Development

We see three key opportunities for accelerating progress in drug discovery and development:

- (i) **Science and technology of drug discovery and development.** There is a pressing need to fill key gaps in the science and technology underlying drug discovery and development. Important areas include validation of biological targets, development and validation of biomarkers for diseases, new types of chemical matter for drug screening, new techniques for drug screening,

¹⁴⁵. To be precise, we mean that the time and cost of projects that begin in the 2020s will be two-fold lower than costs and development times for current projects.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

pharmacogenomics, statistical methods and other areas of emerging science critical to efficient discovery, development, and FDA review of drugs.

- (ii) **Execution of clinical trials.** There is a pressing need to increase the efficiency of clinical trials in the United States. New models could include standing clinical trials networks with efficient IRB review and protocol standardization; pre-accredited sites, including the integration of community practitioners; effective patient accrual, management and retention; the use of Bayesian and adaptive protocols where feasible; high-quality integrated information systems that enable efficient data management, pooling and analysis across sites; standing capabilities to manage patient specimens; and accountability mechanisms for execution of timely, high-quality, and ethically sound clinical studies suitable for new drug registration.
- (iii) **Clear development paths for innovative medicines.** It is important that innovators have clarity about the nature of the clinical evidence that will be necessary to support FDA approval of a drug. Because it is difficult for the FDA to anticipate and analyze the full range of development pathways for innovative medicines in a timely fashion, there may be effective models that engage the biomedical community in identifying needs, analyzing approaches, and achieving consensus. Such efforts could speed the FDA's ability to make decisions and provide necessary guidance.

Addressing these opportunities will require actions both by the Federal Government and by the larger non-Federal community.

Federal action to support innovation in drug development. In December 2011, the Federal Government took two major steps aimed at advancing innovation in drug development.

- The Federal Government created and funded the National Center for Advancing Translational Sciences (NCATS) at the NIH. Appropriately, the mission of NCATS is not to develop pharmaceuticals per se. Rather, NCATS will fund research designed to overcome key challenges in translational research, including (1) creating new biological concepts, chemical methods, and general technologies for the discovery, development, testing, and implementation of therapeutics and diagnostics and (2) demonstrating their feasibility. In addition, NCATS can play an important role in training of translational researchers.¹⁴⁶ Before the creation of NCATS, the NIH had no systematic approach to funding the underlying science and technology of drug development. PCAST applauds the creation of NCATS and urges Congress to support the President's budget request for the new entity, including the authorized Cures Acceleration Network.
- The Federal Government also provided its first funding for the Reagan-Udall Foundation (RUF). RUF is a Congressionally mandated nonprofit (501(c)(3)) organization whose purpose is to support the mission of the FDA, by helping to equip FDA staff with the highest caliber regulatory science and technology in order to enhance the safety and effectiveness of FDA regulated products. RUF was authorized by Congress in 2007, but did not receive Federal funding until FY 2012.

146. Meagher, E.A. and FitzGerald, G.A. "Efficient drug approval and monitoring must rely on sound regulatory science." *Nat. Med.* 2011; 17, 1535 doi:10.1038/nm1211-1535.

Investments in basic biomedical research. It is important to remember that the creation of therapies rests on advances in basic biomedical research, which have depended on robust Federal funding. The Obama Administration provided a substantial boost to the budget via the American Recovery and Reinvestment Act, which temporarily offset previous erosion of the NIH budget from 2003-2008. But sustained investment in both NIH and other science-based agencies will be needed in the future to take advantage of the extraordinary research opportunities that lie before us.

Recommendation 1: Support Federal Initiatives to Accelerate Therapeutics

Public investment is a critical component of the ecosystem that propels innovation in drug discovery, development, and evaluation.

- (i) The Federal Government should strongly support funding for basic biomedical research by increasing the NIH budget to allow for new and further research on the underlying basis of disease and therapeutics.**
- (ii) The Federal Government should vigorously support the newly created National Center for Advancing Translational Sciences (NCATS) at the NIH.** In particular, Congress should support the President's budget request for NCATS, including fully funding the authorized Cures Acceleration Network.
- (iii) The Federal Government should vigorously support the Reagan-Udall Foundation (RUF).**

Broader partnership. While the Federal Government can play an important role in accelerating innovation in drug discovery and development through NCATS and RUF, these efforts cannot alone suffice. Many observers, from academia, government, and the biopharmaceutical industry, have argued for the importance of shared, precompetitive efforts aimed at improving the entire drug development process.

We believe that most of the critical needs in drug development cannot be addressed by individual actors or sectors, but rather require a strong partnership involving—and driven by—the larger non-Federal community, including industry, academic researchers, patient and consumer groups, physicians, and insurance companies. Each stakeholder community brings a distinct and important focus. Industry brings experience about the practical realities of drug development, as well as unique scientific and organizational capabilities for tackling projects. Physicians bring critical perspectives about the use of drugs in practice. Academic researchers bring a focus on general approaches with broader applicability than individual commercial projects. Insurers bring a much-needed focus on the value of drugs in promoting health outcomes. And, patients bring a unique perspective on therapeutic needs, as well as an important sense of urgency.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

The most critical needs include:

- (i) **Filling key knowledge gaps.** As described above, major advances are needed in the science, technology and methodologies of drug discovery and development. Examples include systematic approaches for validation of biological targets, development, and validation of biomarkers for key diseases, new types of chemical matter for drug screening, methods to develop drugs for currently “undruggable” targets, new techniques for drug screening, new approaches to predictive toxicology and pharmacogenomics, and improved statistical methods.

Individual companies will not undertake such efforts at the necessary scale, because the fruits are partially a public good that cannot be fully appropriated by any one funder. Instead, such efforts must be undertaken through shared projects. NIH has a crucial role to play in this work, but cannot fund all of the necessary work through its own budget. Consortia involving shared work and shared funding are needed.

- (ii) **Improving clinical trials capabilities.** As described above, our clinical trials network is inefficient and expensive. There is a need for new models, tools, and capabilities to transform and streamline the testing of new drugs and associated diagnostic tests for FDA review. We need standing clinical trials networks with efficient IRB review; pre-certified sites, including the integration of community practitioners; effective patient accrual, management and retention; high-quality integrated information systems that enable efficient data management, pooling and analysis across sites; ability to manage patient specimens; and rigorous accountability for execution of timely, high-quality and ethically sound clinical studies suitable for registration of a new drug.

One effective model may involve for-profit networks for specific diseases, created by consortia of companies that provide shared support for the ongoing infrastructure and pay for the running costs of their individual trials. Neither the Federal Government nor individual companies can create such networks. Only consortia of parties can do so.

- (iii) **Clarify the development pathway for innovative medicines.** As described above, it is challenging for the FDA to provide, in a timely fashion, guidance documents about development pathways in emerging areas and public letters concerning new tools for drug development. While the ultimate decisions must rest with the FDA, the Agency’s process could be accelerated if diverse experts and stakeholders came together to identify needs, gather relevant scientific information, and develop community consensus in an open and transparent process. There is a need for timely and high-quality work on a wide range of topics. To be credible, such efforts must involve consortia of parties representing a wide range of perspectives and interests.

PCAST believes that a high-level partnership is vital to filling these gaps. While there are a number of organizations and collaborations to work on isolated components of this challenge, there is no overarching framework that allows the most crucial needs to be identified and addressed efficiently. What is required is an entity through which key stakeholders can come together on a regular basis, engaging the highest level of leadership from the various sectors to address the challenges to transforming drug development. The lack of such an entity makes the activation barrier to addressing the needs of this ecosystem very high, and impedes progress toward accelerating innovation in drug discovery and development.

The best way to address the need would be to create a broad-based Partnership to Accelerate Therapeutics involving the bio-pharmaceutical industry; the academic biomedical research and ethics community; physician societies and pharmacists; patient-focused research foundations and advocacy groups; healthcare providers and insurers; and the Federal Government.

We envision four main tasks for the Partnership:

- (1) Identifying key needs and opportunities;**
- (2) Prioritizing these needs and opportunities;**
- (3) Developing detailed plans for shared scientific and technological projects; business and operational plans for clinical trials networks; proposed guidance documents and supporting materials; and other high-quality work products; and**
- (4) Ensuring that projects are launched, by bringing together allies and raising support.**

The Partnership would facilitate the creation of projects, but in general would not itself carry out the projects. In some cases, projects would be performed by existing entities. For example, NCATS would be a natural home for many activities to fill key knowledge gaps. In other cases, new entities might be organized by sets of stakeholders in response to a need. For example, biopharmaceutical companies might form a joint venture to create a clinical trials network.

The Partnership would serve as an umbrella organization that would: engage high-level leadership across key stakeholder organizations on a sustained basis; have a governance structure that ensures that the Partnership is transparent; balances competing interests and benefits the public; coordinate with existing efforts and minimize unnecessary duplication of effort; have a sufficient professional staff, with appropriate expertise; and operate in a business-like and accountable manner. The Partnership would need a sufficient budget to accomplish its goals, provided by the various stakeholders.

We note that there have been a number of successful examples of private and public-private consortia to address major challenges facing an industry. A famous example is the SEMATECH consortium formed in the late 1980s and early 1990s, at a time when the U.S. semiconductor industry was under great stress from foreign competition. Combining private funding from 14 U.S.-based semiconductor manufacturers together with public funding from the Federal Government, SEMATECH supported joint precompetitive research on next-generation technology for integrated circuit memory chips in a shared facility in Austin, Texas. SEMATECH also supported a test facility for tool and equipment suppliers in the semiconductor industry's supply chain to prototype innovations, creating major efficiencies for the companies in the consortia. SEMATECH is generally regarded¹⁴⁷ as having played an important role in the resurgence of the U.S. semiconductor industry. The SEMATECH analogy is not exact: (1) the issues in drug development involve a worldwide decrease in productivity, rather than a threat from more efficient foreign competition, and (2) we do not envision the Partnership to Accelerate Therapeutics to operate its own laboratories or large projects. And, the solutions may require a set of consortia projects rather than a single shared project. Nonetheless, the example demonstrates the power of properly organized and managed precompetitive consortia to dramatically advance an important area in times of stress.

147. Flamm, K. "Economic Impacts of International R&D Coordination: SEMATECH and the International Technology Roadmap," *21st Century Innovation Systems for Japan and the United States: Lessons from a Decade of Change: Report of a Symposium, National Academies of Science and Engineering*. 2009; Van Atta, R., et al, *Semiconductor Dependency*, Institute for Defense Analyses, 1988.

Recommendation 2: Catalyze the Creation of a Broad-Based Partnership to Accelerate Therapeutics

The Federal Government should encourage and participate in the creation of a broad-based Partnership to Accelerate Therapeutics, engaging a range of stakeholders including: patient-focused research foundations and advocacy groups; the bio-pharmaceutical industry; the academic biomedical research and ethics community; physician societies and pharmacists; healthcare providers and insurers; and the Federal Government, including the FDA and NIH. The Partnership should be a non-Federal entity that brings together high-level leadership in a public-private partnership.

Mission. The Partnership's mission should be to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs.

Focus. The Partnership should focus initially on identifying needs in three major areas: (1) Filling key knowledge gaps in the science, technology, and methodologies underlying drug discovery and development; (2) Improving clinical trials capabilities, including through new kinds of clinical trials networks; and (3) Clarifying the development pathway for innovative medicines, including through convening the community to provide input on guidance documents.

Activities. The Partnership should have four main activities: (1) Identifying key needs and opportunities; (2) Prioritizing these needs and opportunities; (3) Formulating specific solutions and developing detailed plans, including for shared scientific and technological projects, business and operational plans for clinical trials networks, proposed guidance documents and supporting materials, and other high-quality work products; and (4) Ensuring that projects are launched, by bringing together allies and raising support.

The Partnership would facilitate the creation of projects, but in general would not itself carry out the projects. Instead, projects would be performed by existing entities (such as NCATS or specific consortia, such as the Biomarkers Consortium) or by new entities organized by sets of stakeholders in response to a need (such as a joint venture to create a clinical trials network).

Structure. The Partnership should: engage the high-level leadership across key stakeholder organizations on a sustained basis; have a governance structure that ensures that the Partnership is transparent, balances competing interests, and benefits the public; coordinate with existing efforts and minimize unnecessary duplication of effort; have a sufficient professional staff, with appropriate expertise; and operate in a business-like and accountable manner. The Partnership would need a sufficient budget to accomplish its goals, which should be provided by the various stakeholders.

There is currently no entity that serves these important goals. The mission cannot be appropriately performed by Federal entities such as the NIH, the FDA, the Foundation for the NIH, or the RUF (although these entities may have a central role in carrying out some of the projects identified and prioritized). This is because each of these Federal entities is dedicated to its own agency-specific mission, rather than to the needs of the drug discovery, development, and evaluation ecosystem as a whole.

The closest match, in terms of broad mission, is the Institute of Medicine Drug Discovery, Development and Translation (IOM Drug Forum). The IOM Drug Forum is a convening body that brings together leaders from

V. A PATH FORWARD

private sector sponsors of biomedical and clinical research; Federal agencies sponsoring and regulating biomedical and clinical research; foundations; the academic community; consumers; and Federal and private health plans to discuss issues related to the full drug development pipeline — from drug discovery and regulatory approval to translation of research into clinical practice. It undertakes the first of the four activities envisioned for the Partnership (identifying key needs and opportunities). However, the IOM Drug Forum does not currently engage in the more action-oriented activities envisioned for the Partnership (prioritizing, developing detailed business plans for projects, and ensuring that projects are launched). Moreover, it lacks an adequate staff, budget, and organizational structure to carry out the envisioned activities.

To be successful, the Partnership would need:

- **Board of directors.** The board would consist of senior leaders from stakeholder groups, with responsibility for setting direction, making decisions about project priorities, and overseeing professional staff. Certain key stakeholder groups could play an ongoing role in the selection of the board on an ongoing basis (for example, key industry organizations, patient and consumer organizations, medical philanthropies, the FDA and the NIH). It will be important that the Partnership's board be balanced in representation among stakeholders, and that voices representing the broader public interest have an ample role in governance.
- **Professional staff.** The Partnership should have a president and staff with extensive experience in drug discovery, development, and evaluation. The staff should include administrative staff (to support the work of the Partnership), core scientific staff (to work with experts inside and outside the Partnership to identify, prioritize, plan, and help launch projects) and project management staff (responsible for ensuring that key projects are launched). A staff of at least 30-40 people would likely be required to fulfill the goals.
- **Funding.** An annual budget of at least \$10-15 million would likely be required to fulfill the goals. Funding would come primarily from key corporate and non-profit organizations.

There are several ways in which the Partnership could be created.

One approach would be for the Partnership to be organized and hosted under the auspices of a respected non-Federal entity. One possible entity would be the IOM. As the health arm of the independent, non-profit, Federally chartered National Academy of Sciences, the IOM is a well-respected, neutral institution with the expertise and the standing to convene parties from all sectors. The IOM's traditional role has been to organize committees and "think tanks" that produce excellent reports. To be a successful organizing body for the Partnership, it would need to go beyond this traditional role to organize an operational entity that would (1) serve the public interest, on behalf of a diverse range of stakeholders, (2) be organized and staffed in a business-like manner, and (3) develop business plans for and help launch projects on a sustained basis.

Another possibility would be for the Partnership to be organized and hosted by a major non-profit biomedical foundation. The Partnership could be organized jointly by IOM and a biomedical foundation, or by other suitable organizations. The choice of entity to organize or host the Partnership should be made by the stakeholders.

An alternative approach would be for the Partnership to be established as an independent non-profit entity with 501(c)(3) status. Under this model, a respected non-Federal entity could shepherd the creation of the Partnership by (i) convening key stakeholders to agree on a governance structure for the Partnership and (ii) selecting the initial board. The non-Federal entity could potentially play an ongoing oversight role to ensure that the Partnership fulfills its mission, and could potentially provide services to the Partnership if needed. The National Academy of Sciences (of which the IOM is a part) could play such a role.

Various stakeholders, including Federal agencies, have expressed strong support for and a sense of urgency about organizing a Partnership. The time required to organize the Partnership may differ under various models and may thus influence the preferred approach.

In addition to the Partnership spanning stakeholders from multiple sectors, we believe it could be useful for biopharmaceutical companies to create a joint entity focused on pre-competitive R&D-related efforts. Such an entity could help coordinate industrial engagement in the Partnership and might carry out some of the joint projects identified by the Partnership, such as new types of clinical trials networks.

B. Improving Drug Evaluation

The FDA's mission is to ensure that the American people gain access rapidly to new drugs that are safe and effective, while being protected from drugs that are not. The agency can fail in two ways: by being overly cautious (e.g., unreasonably delaying the approval of life-saving drugs) or by being insufficiently cautious (e.g., approving drugs that are ineffective or cause great harm). The latter failure mode gets the most publicity, but the former can be just as serious.

How can the FDA accelerate the flow of innovative drugs? We believe that the best solution is to enable the FDA to be more forward-leaning by optimizing the scientific and regulatory tools for minimizing and managing risk and for improving drug efficacy. We recommend two major initiatives concerning the drug approval process and suggest exploring a third approach.

Expanding the Use of Accelerated Approval

As described in Chapter 4, the FDA has authority to grant Accelerated Approval for a drug “on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity,” with the requirement that the sponsor conduct follow-up studies to verify the clinical benefit. Demonstrating a favorable impact on a marker predictive of clinical outcome can be much faster and less expensive than demonstrating impact on the clinical outcome itself. Of course, this is valuable only if the surrogate is actually a valid predictor of the relevant clinical outcome. (For a detailed discussion of this topic, see Box on Surrogate Endpoints and Intermediate Clinical Endpoints in Chapter 3.)

Accelerated Approval involves making an educated guess. For a novel endpoint, there is no way to be certain that it will be a valid predictor of clinical benefit; errors will occur. However, for a serious disease with no good treatments, early access for patients, coupled to a requirement for ongoing knowledge-generation represents a good compromise. For traditional approvals and for diseases that do not meet

the standard of being life-threatening or serious and with an unmet need, surrogate endpoints must have much greater validity and certainty associated with them.

Achieving the full benefits of the Accelerated Approval pathway requires that: surrogate and clinical predictors are chosen wisely; uncertainties are communicated to the public; confirmatory studies are conducted expeditiously; and post-marketing safety and effectiveness is monitored carefully. We believe that the Accelerated Approval pathway can be improved by optimizing these components and fully implementing existing statutory authority.

The FDA should expand the scope of acceptable endpoints used to approve drugs for serious or life-threatening diseases with unmet needs. Under current law, the FDA has considerable discretion in deciding whether a surrogate or intermediate clinical endpoint is “reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict” clinical benefit. At one extreme, the FDA might be highly risk-averse, requiring near-certainty that the surrogate or intermediate endpoint will translate to clinical benefit. At the other extreme, the Agency might accept endpoints that are simply correlated with disease outcome or plausibly related to disease outcome based on current scientific understanding. Neither extreme would serve the public well. The FDA’s interpretation of “reasonably likely...to predict” can have a major impact on the pace of medical innovation and on patient safety. (See box on surrogate endpoints in Chapter 3 for further discussion.)

Historically, the use of Accelerated Approval has been primarily used in a limited number of therapeutic areas—principally, HIV/AIDS, cancer, and inhalation anthrax¹⁴⁸ (87 percent of cases). And, Accelerated Approval has been granted typically on the basis of surrogate endpoints (laboratory measures or tests), with intermediate clinical endpoints¹⁴⁹ being used relatively rarely (on average once per year).

We believe that the Nation would benefit if the FDA were to expand the use in practice of acceptable indicators to other serious or life-threatening diseases, especially by encouraging broader use of intermediate clinical endpoints that have a reasonable likelihood of predicting clinical benefit. These are distinct from surrogate endpoints (lab measures, radiographic imaging, or quantitative tests), in that these are interim measures of how a patient feels, functions, or survives. Intermediate clinical endpoints provide some degree of clinical benefit to patients but are short of the desired, long-term meaningful clinical outcome from a treatment.

FDA staff have suggested that possible intermediate clinical endpoints suitable for Accelerated Approval might include, for example:

- Using improvement in minimal cognitive impairment in likely early-stage Alzheimer’s patients¹⁵⁰ as a predictor of delayed progression of the disease, rather than waiting to assess progression.

148. GAO. “FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints”; Oct 26, 2009. GAO-09-866.

149. Intermediate clinical endpoints are measures of how a patient functions, feels or survives. To be used for Accelerated Approval, there should be a reasonable likelihood that an improvement in an intermediate clinical endpoint will predict a meaningful change in a desired outcome of disease.

150. Such a study might focus on patients with early symptoms and the highest-risk genotype (e.g., homozygous carriers of the ApoE4 allele) Source: Farrer, L.A., et al. “Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium.” *J. Am. Med. Ass.* 1997; 278(16):1349-56.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

- Using improvement in isolated muscle strength in patients with a muscular dystrophy as a predictor of benefit, rather than waiting to assess overall deterioration of the patient.
- Using clearance of drug-resistant organisms as a predictor of likely clinical benefit, rather than waiting to measure overall survival rate.
- Using measures of the amount of air that a patient can exhale by force (a measure of lung capacity known as forced vital capacity) or functional motor tests as an endpoint for predicting a drug's likely impact on two serious diseases lacking good treatments: spinal muscular atrophy, a genetic neuro-muscular disease, and amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease.

These examples are simply intended as possible illustrations. Whether they would truly be suitable endpoints for Accelerated Approvals would need to be determined by the FDA. PCAST does not specifically advocate the use of these intermediate clinical endpoints, but they have been suggested to us by the Agency as possible candidates.

Intermediate clinical endpoints can be quite powerful, but they can also fail. Broader use of intermediate clinical endpoints for serious or life-threatening diseases with unmet needs should be accompanied by the requirements that (1) post-market trials are conducted to test whether the drug's effect on the endpoint translates into significant clinical benefit, (2) the approved drugs are demonstrated to be safe enough to have a favorable risk-benefit ratio for the patient population, and (3) the FDA has adequate tools to withdraw approval for drugs that fail to meet these criteria.

We recognize that there is some risk in employing predictors, but we believe that the opportunities for progress against serious or life-threatening diseases without good treatments justify taking prudent risks.

The biomedical research community should take a more active role in determining whether endpoints are reasonably likely to predict clinical benefit. While the FDA has the authority to decide whether an endpoint is suitable for drug approval, we believe that the decision should largely reflect the consensus of the scientific community. The scientific community should play a more active role in developing and evaluating whether new surrogate endpoints and intermediate clinical endpoints have a reasonable likelihood of predicting clinical benefit for serious or life-threatening diseases with unmet need. The FDA should engage the community in identifying the needs for and weighing the value of possible predictors. The best decisions will emerge from transparent discussion about these judgment calls.

The FDA should clarify its guidance to drug sponsors concerning Accelerated Approval in general, as well as with respect to the acceptability of specific indicators. Drug developers have expressed frustration that it is difficult to get clear and timely answers concerning the acceptability of specific predictors for Accelerated Approval. Without such clarity, the risk of employing such predictors during the lengthy drug-development process is often too great to justify significant investment. While the FDA must proceed thoughtfully in approving predictors, the risks will be mitigated provided that confirmatory studies are performed in a timely manner by drug sponsors.

The FDA should strengthen its enforcement of the requirement for confirmatory studies. If the FDA is to expand the range of endpoints for Accelerated Approval, it must also ensure that sponsors perform the confirmatory studies to verify the clinical benefit and safety of drugs approved under Accelerated Approval and to validate the endpoints for use in future studies. As noted in Chapter 4, there is evidence

that historically the industry has not always fulfilled and/or that the FDA has not adequately tracked and enforced requirements that companies complete confirmatory studies required for Accelerated Approvals to demonstrate efficacy and thereby verify the drug's clinical benefit.¹⁵¹ The FDA should strengthen its enforcement of these requirements, including using its existing authority to withdraw approval or impose penalties where confirmatory studies have not been completed in a timely fashion.¹⁵² To ensure that post-marketing studies are completed in a timely manner, new mechanisms might be considered—for example, if studies are not completed, the approval will be presumed to sunset or expire (absent an extension by the Agency) or that the sponsor will have a contractual obligation to pay for a third party to carry out the study.

Recommendation 3: Expand the Use in Practice of FDA's Existing Authorities for Accelerated Approval and Confirmatory Evidence

The FDA should make fuller use of authorities previously granted by legislation and not yet fully utilized.

- (i) **The FDA should expand the use in practice of its existing authority for Accelerated Approval.** FDA should direct its staff, across all divisions, to make full use of the Accelerated Approval track for all drugs meeting the statutory standard of addressing an unmet medical need for a serious or life threatening illness and demonstrating an effect on a clinical endpoint (other than survival or irreversible morbidity) or on a surrogate endpoint that is reasonably likely to predict clinical benefit.
- (ii) **The FDA should issue clear guidance concerning the types of new drug applications that would be eligible for Accelerated Approval.** The guidance should clarify the definition of unmet medical need, serious illness, and suitable clinical or surrogate endpoints, particularly intermediate clinical endpoints.¹⁵³
- (iii) **The FDA should actively engage the biomedical community in the development and evaluation of specific predictors, and should provide clear, timely, and transparent guidance to sponsors about the acceptability of specific surrogate and intermediate endpoints.** The scientific community should play a central role both in identifying interim endpoints and in weighing whether it is reasonable to use them as predictors of clinical outcome based on available knowledge and medical need. The FDA should make timely decisions based on available evidence, recognizing that the cost of indecision is high and the risk of decisions is mitigated by the requirement for confirmatory studies.

151. However, some observers have noted that the FDA has often not withdrawn approval when studies go uncompleted, in part because it is practically or politically untenable to do so once a drug is on the market and being used by a patient population in need. An example is midodrine, approved under Accelerated Approval for symptomatic orthostatic hypotension in 1996 with a condition for confirmatory studies that have still not been fulfilled by the sponsor.

152. We note that, in some cases, recruiting patients to randomized trials may be difficult due to the nature or prevalence of the disease. For such cases, other types of studies or evidence (including those that use historical controls or pharmacoepidemiological methods) may need to substitute for randomized controlled trials in the post-market phase.

153. Under Section 901 of FDASIA, which amends Section 506(c) of the Federal Food, Drug & Cosmetics Act, FDA will issue draft guidance on accelerated approval within 1 year of enactment and final guidance and, as necessary, amendment of the regulations governing accelerated approval with 1 year after the draft guidance. We recommend that this guidance address the expanded use in Recommendation 3 (i).

(iv) The FDA should fully enforce the requirement for confirmatory studies. When granting Accelerated Approval for a drug, FDA should make full use of its existing authorities to enforce post-marketing requirements. This includes the ability to withdraw approval of drugs and to ensure that appropriate clinical studies (including well-controlled trials) are completed in a timely manner following initial approval, toward the goal of expanded or restricted indications depending on the results of these studies. If necessary to ensure that confirmatory studies are undertaken, Congress should consider such mechanisms as presumption of expiration of approval if confirmatory studies are not performed within a specified period.

With respect to ensuring the performance of confirmatory studies for drugs approved under Accelerated Approval, we note that insurers may have an important role to play by tying long-term reimbursement to studies demonstrating efficacy.

Approval for Special Medical Use

For some serious or life-threatening conditions, a relatively small and rapid clinical trial may suffice to demonstrate the safety and efficacy of a drug in a specific subgroup of patients who have a serious, high-risk manifestation of a common condition or who are at especially high risk for developing a serious disease. Yet, before approving the drug, the FDA believes it has the legal responsibility to consider the overall benefit-risk balance of the drug—including the potential to cause harm in a larger population with milder manifestations or at lower risk. The FDA's need to address such possibilities could significantly delay the availability of the drug to patients in the subpopulation. Yet there is a need to develop further knowledge about the drug before it is prescribed widely.

One example is a drug that has a favorable benefit-risk balance for treating patients with morbid obesity. Before approving the drug, the FDA weighs the potential harm that could arise from the possibility that physicians would widely prescribe the drug off-label to treat mildly obese patients wishing to lose 10 pounds. Under such circumstances, the Agency tends to require that a sponsor conduct large clinical trials to address the more complex benefit-risk issues in such populations.

If there were a pathway under which (1) a sponsor could propose, early in the development process, to study a drug initially for a narrow indication and (2) the likelihood that the drug would be used in a broader population were substantially reduced, the FDA believes it could responsibly approve the drug based on the data concerning the subpopulation with a serious manifestation of the conditions or at especially high risk, and serious need. There would be several advantages to such a pathway. Drug sponsors could propose faster and smaller clinical trials for initial market approval, which would benefit patients in need of therapies or prevention (as well as, potentially, innovators in need of initial financial return to support further development).

Another important example is the development of drugs to treat bacteria resistant to current antibiotics, which is an urgent medical need. A small clinical trial might rapidly demonstrate a favorable benefit-risk balance in patients with life-threatening infections caused by antibiotic-resistant bacteria. Yet, the FDA would be concerned about the drug becoming widely used as a broad-spectrum antibiotic in a broad population. First, it would be necessary to establish the benefit-risk balance. This could involve non-inferiority studies involving several thousand patients. Second, widespread use would soon select for the emergence and spread of bacteria resistant to the new drug, undermining its clinical benefit to the

public. Good “antibiotic stewardship” would involve limiting the use of the new drug to drug-resistant cases. Currently, there is not a mechanism to encourage that a new drug will only be used against organisms resistant to standard therapies.

As discussed in Chapter 4, the FDA believes its current REMS authority is not well-suited to this task. REMS is a cumbersome tool and has to date primarily been used to address known risks related to an approved indication, rather than uncertainty about, or knowledge of potential risks to a broader population. In addition, REMS does not provide a good mechanism to deal with future public health risks from clinical use not directly resulting from the drug, such as the emergence of drug-resistant bacteria from the broad clinical use of antibiotics.

One solution might be for Congress to give the FDA direct authority to restrict the right of physicians to prescribe such drugs off-label. However, for a variety of reasons, we do not believe that this approach is workable or desirable.

A better solution might be for the FDA to implement a mechanism under which sponsors could voluntarily request to develop a new drug for initial approval under a new designation: Special Medical Use (SMU). The sponsor would (1) propose a development process to address the benefit-risk balance in a high-risk subpopulation, using the same standards for efficacy and safety as for existing approval pathways (traditional or accelerated) and (2) demonstrate that clinical trials in the larger population of patients would require much longer time periods to complete or would not be feasible.

The SMU designation would signal to physicians and insurers that, based on current evidence, the FDA considers the drug to be inappropriate for use outside the specific subpopulation. While not forbidding off-label use by physicians, the designation would need to strongly influence clinical decisions of physicians and formularies, reimbursement decisions by health care payors and practices of malpractice insurers. Provided that it decreases the likelihood of off-label use, the SMU designation could enable FDA to grant approval consistent with its obligation to weigh the overall benefit-risk balance. Following initial approval under SMU designation, sponsors could apply for subsequent approval without the SMU designation by conducting further clinical studies that address the risk-benefit balance in broader patient populations.

PCAST is unclear whether the FDA (1) can create an SMU designation through new regulations under its existing statutory authority or (2) would require additional authority to do so. Some experts believe that FDA has adequate authority to act under the FDA Amendments Act (FDAAA 2007) and could promulgate regulations to enact this pathway and designation. Others believe that, even if the FDA does have sufficient authority, it would be valuable and important if Congress were to explicitly authorize this pathway, or at least, endorse its creation.

PCAST endorses the creation of an SMU designation. We emphasize, however, that the SMU designation will only succeed if it is implemented in such a way as to strongly influence behavior. Payors may play a central role in shaping behavior through their decisions about reimbursement policy, including through public payor provisions for “coverage with evidence development” and analogous policies by private insurers.¹⁵⁴ Accordingly, payors should be actively engaged in discussions about the SMU designation.

154. Specifically, reimbursement policies can be structured to ensure that drugs approved through the SMU designation are generally prescribed in accordance with the FDA approved indications through payer coverage policies that limit reimbursement to clinical use according to the approved indications. Reimbursement policy can also support the implementation of required post-approval studies through the use of “coverage with evidence development” and other policy mechanism that link reimbursement to the enrollment of patients in clinical studies. See: www.cmtynet.org/coverage-with-evidence-development.

Recommendation 4: Create a New Pathway for Initial Approval of Drugs Shown to be Safe and Effective in a Specific Subgroup of Patients

The development of new medicines for the treatment and prevention of serious chronic diseases and conditions, such as Alzheimer's disease, obesity, and drug-resistant bacterial infection is an important public health need. For some drugs, clinical trials may be able to demonstrate the safety and efficacy of a drug in a specific subgroup of patients who have a serious, high-risk manifestation of a common condition (such as morbid obesity, or bacterial infection resistant to standard antibiotics) or who are at especially high risk (such as patients with auto-antibodies that point to high-risk for development of Type 1 diabetes) long before it is possible to determine the more complex benefit-risk balance for broader groups with milder conditions or less risk (such as overweight or ordinary bacterial infection). Currently, FDA may not grant approval without extensive clinical trials in the larger population due to concerns about safety risks resulting from possible off-label use in broader groups. It would be desirable to have a pathway under which such drugs could rapidly reach high-need patients while reducing the risks from wider use of the drug. In the case of antibiotics, there would also be clear public health benefits to limiting the use of new antibiotics effective against drug-resistant bacteria, to stave off the emergence of drug-resistant strains.

- (i) The FDA should implement a drug approval pathway under which sponsors could propose, early in the development process, to study a new drug for initial approval under a designation of Special Medical Use (SMU).** Under this pathway, sponsors could request and the FDA could approve drugs in which the usual criteria for approval (traditional or accelerated) were met in a subgroup of patients with a serious, high-risk manifestation of a common condition, but in which it was not feasible to determine in a timely manner the benefit-risk balance for broader patient use. This designation and pathway would be sought early in the development process to allow the sponsor and the FDA to agree upon a more narrow development program than required for traditional approvals. This pathway would not be intended as an alternative means to approve a drug that is late in development or in the review and approval process. Sponsors could subsequently apply for approval without the SMU designation by providing clinical evidence of the benefit-risk balance in the broader patient population.

The purpose of the SMU designation would be to send a clear and effective signal to patients, physicians, payors, and malpractice insurers that the drug should be reserved for use in the specific subgroup of patients. The SMU designation would not forbid off-label use, but would be intended to affect the likely usage by shifting responsibility to educated prescribers and payors. In doing so, it would shift the overall benefit-risk balance and allow the FDA to responsibly approve drugs intended for patients with the serious manifestation.

- (ii) If the FDA determines that existing statutory authority is sufficient for the Agency to implement the SMU designation, it should do so through new regulations.**
- (iii) If the FDA concludes that existing statutory authority is insufficient or that Congressional endorsement is desirable, the Congress should pass legislation that clearly authorizes and encourages the FDA to create the new pathway.**

We emphasize several important points about the proposed SMU pathway:

- (1) The pathway would not give the FDA authority to regulate the practice of medicine. Responsibility for prescribing would rest with informed physicians.
- (2) The pathway would be an option for companies to elect and pursue early in a development program, and would not be imposed by the FDA.
- (3) For certain categories of drugs, it might be appropriate for Congress to adjust the exclusivity period for drugs with SMU designation to reflect that they are being prescribed to a limited population. This could be appropriate in instances where a drug's use is being limited for public health considerations, such as for a drug to treat bacteria resistant to standard antibiotics.

Adaptive Approval

Various thoughtful commentators have proposed approaches for accelerating the availability of innovative drugs to patients that go beyond the specific approaches embodied in Recommendations 3 and 4. Broadly termed “adaptive approval,” these approaches would involve a series of approval stages that would iteratively expand the market for a drug based on the evidence generated about the drug's risks and benefits. Adaptive approval contrasts with the binary approach to drug approval that predominates today, whereby a drug is approved or rejected based on a given data package at a single moment in time; the binary approach fails to adequately acknowledge and signal evolving knowledge about risks and benefits. Accelerated Approval and SMU can be viewed as specific instances¹⁵⁵ of the concept of adaptive approval.

Under an adaptive approval approach, an initial approval would be provided based on a body of evidence that shows a favorable benefit-risk balance for a defined group of patients. During an initial (provisional) approval phase, patient access to drugs would be managed to limit exposure to risks while more information on the efficacy and safety of drugs in use is gathered. Emerging evidence would be used to modify approval status and would be communicated to patients, prescribers, and health care payors. Drugs would be evaluated across their lifecycle, with iterative phases of evidence gathering and reassessment. For this reason, adaptive approval would require greater evidence-generation for drugs once they are in use than is currently done under existing approaches to approval.¹⁵⁶ Research and pilot studies concerning adaptive approval are being undertaken by regulators in other nations, including Health Canada, the EMA, and the Health Sciences Authority of Singapore. The MIT Center for Biomedical Innovation is working with these regulatory agencies to develop pilot projects.

For adaptive approval to be a viable approach, it would be necessary to have mechanisms to ensure that (1) drugs are prescribed largely to patients for which they have been approved at the time; (2) evidence about drugs' risks and benefits is generated on an ongoing basis, including through randomized controlled studies, pharmaco-epidemiological data, and robust monitoring after initial approval; and (3) drugs for which follow-up studies and monitoring are not completed or demonstrate an unfavorable risk-benefit balance can be readily removed from the market.

155. Though possibly incomplete in the range of tools applied to learning about the drugs across their life-cycle.

156. Eichler H.G., Oye, K., et al. “Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval.” *Nat. Clin. Pharmacol. Ther.* 2012; 91:3, p. 426-437.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

These requirements pose challenges in the context of the highly decentralized U.S. healthcare system. To be workable, a solution would likely need an appropriate balance of incentives and restrictions, such as:

- **Early access to market.** Drug developers would gain earlier market access for restricted indications, which would then be expanded as additional evidence was generated demonstrating a favorable benefit-risk in additional indications or populations.
- **Labeling, warning, and restrictions.** The FDA would have a stronger and clearer labeling system, including stating that there is no evidence to justify prescribing the drug outside the specific populations for which it has been approved and that it would currently be irresponsible, in general, to do so based on current knowledge, owing to possible serious risks. The FDA might also require certain tests, robust monitoring, and reporting associated with prescribing the drug. To be effective, these steps would need to be strong enough to influence behavior of physicians, payors, and malpractice insurers with respect to the use of drugs in initial phases of approval. These restrictions would be lifted as knowledge about the drug's efficacy and safety was expanded.
- **Advertising.** The FDA might, for example, require and strictly enforce that advertisements disclose current limitations of knowledge about the drug.
- **Withdrawal of drugs.** The FDA might require more robust tools for removing drugs from the market when studies fail to confirm the expected benefit-risk balance or when critical knowledge is not generated via monitoring and other tools.
- **Economic incentives.** In order not to seriously erode economic returns to drug developers, provisions might eventually be needed to adjust exclusivity periods to partially offset the time during which drugs are marketed under strong restrictions.

Many issues would ultimately need to be worked out to create a viable system. PCAST believes that it would be useful for the FDA, in consultation with stakeholders including patient groups, academia, industry, and payors to explore ways, within existing drug approval pathways, to carry out pilot projects to explore approaches for adaptive approval.

While we favor pilot projects to explore adaptive approvals, we distinguish this from recent proposals to implement adaptive or "progressive" approval approaches through legislation. One recent legislative proposal, for example, contemplated granting provisional approval to drugs addressing urgent patient needs for a serious or life-threatening condition based on less clinical evidence than required under current standards for traditional or Accelerated Approval, with a requirement of ongoing knowledge generation about the drug. For a variety of reasons, PCAST does not think this approach is currently tenable. Serious questions would need to be addressed about appropriate evidentiary standards, protection of patient's rights and interests, and mechanisms to ensure timely clinical studies and withdrawal of drugs to make such a pathway viable.

PCAST, therefore, does not recommend that the Federal Government pass at this time new legislation to enact adaptive or progressive approval, nor does it recommend at this time creating a new drug approval pathway. Research and multi-stakeholder discussion is required to determine what regulatory tools and incentives are required to shift towards a more adaptive drug approval and monitoring system.

Recommendation 5: Explore Approaches for Adaptive Approval Via Pilot Projects Under Existing Pathways, but Do Not Create New Adaptive Approval Pathways Through Legislation.

The FDA, in consultation with patient advocacy groups, the medical community, payors, and drug sponsors, should explore adaptive approaches to approval. A study should be undertaken, involving all stakeholders, to address issues including: potential evidentiary standards, protection of patient safety and rights, and mechanisms to ensure timely post-marketing clinical studies and withdrawal of drugs. The study should also outline the regulatory tools and incentives that would be needed to ensure adaptive approaches balance safety and innovation. **PCAST recommends that the FDA undertake pilot projects within existing approval pathways.**

Some parties have proposed that Congress pass new legislation to create a new regulatory pathway at FDA for “adaptive” or “progressive” approval of drugs, based on limited initial data coupled to ongoing knowledge generation across the life-cycle of the drug. While there are potential benefits, there are many unanswered questions about how such a pathway would work in practice and whether it would adequately protect the public from unsafe or ineffective treatments.

PCAST recommends against passing at this time legislation to create a new framework for “adaptive” or “progressive” approval.

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

For comparison purposes, the various approval mechanisms discussed above are summarized in the table below.

Table 1: Explanation of Approval Mechanisms Discussed in the Report

Traditional Approval

Applicability: Any medical condition.

Standard for Approval: Substantial evidence¹⁵⁷ from adequate and well-controlled trials demonstrating a favorable benefit-risk balance.

Accelerated Approval

Applicability: Serious or life-threatening conditions with unmet medical need.

Standard for Approval: Substantial evidence from adequate and well-controlled trials demonstrating impact on a surrogate endpoint or intermediate clinical endpoint reasonably likely to predict clinical benefit.

Potential benefit to stakeholders: Earlier access to drug for patients and to market for sponsors; generation of targeted knowledge about validation of surrogate or intermediate clinical endpoint.

PCAST Recommendation: Expand the use in practice to more disease areas and to greater use of intermediate clinical endpoints. Requires no new legislation.

Special Medical Use

Applicability: Serious or life-threatening conditions with unmet medical need.

Standard for Approval: Substantial evidence from adequate and well-controlled trials demonstrating impact on a clinical outcome (traditional) or a surrogate endpoint or intermediate clinical endpoint likely to predict clinical benefit (accelerated) in a patient subgroup with a serious manifestation of a condition or at especially high risk of developing a serious disease.

Potential benefit to stakeholders: Earlier access to drug for patients in defined group and to market for sponsors; generation of knowledge about drug before wider release; greater assurance that off-label prescribing will not pose danger to patients.

PCAST Recommendation: Create new approval mechanism via regulation or legislation. (See Recommendation text.)

Adaptive Approaches to Approval

Applicability: A broad set of approaches involving a series of approval stages that would iteratively expand the market for a drug based on the evidence generated about the drug's risks and benefits. Many aspects remain to be defined.

Potential benefit to stakeholders: Potential for earlier access to drugs for patients in a defined group and to market for sponsors; generation of knowledge about drugs (including real-world performance) before wider release, and broader scope of learning about safety and efficacy following each iterative approval; reduced number of patients exposed to risk during the greatest period of uncertainty; greater transparency to public about drugs and uncertainty.

PCAST Recommendation: Explore further through collaborative research, pilots, and discussions. Do not pass legislation or enact a new approval pathway at this time.

157. In 1997, Congress created an alternative standard for statutory evidence (FDAMA 115) and granted FDA the authority to approve new drugs with a smaller evidence base than typically required for approval. The provision allows the FDA to approve drugs based on "one adequate and well-controlled clinical trial with confirmatory evidence". However, this provision has been rarely used and has been largely confined in practice to rare or orphan diseases, where there are clear logistical challenges to performing more than a single trial. Although the FDA has the legal authority and flexibility to approve other drugs based on a single trial with confirmatory evidence, the challenge for the Agency and for the biomedical community is to define the conditions under which such approvals can be granted without eroding the protection of patients from unsafe or ineffective medicines.

C. Monitoring and Communications about Benefits and Risks

The FDA's ability to approve drugs would be enhanced if (1) surveillance systems had greater ability to detect safety issues in marketed drugs and (2) patients had greater understanding about the uncertainties of risks and benefits of marketed drugs.

The FDA should improve systems to communicate the uncertainty about marketed drugs. Physicians and patients should have clear knowledge of the uncertainties surrounding a drug. This is true for all drugs, but is especially important for drugs approved under Accelerated Approval (where clinical benefit has not been definitively demonstrated) and drugs tested only in limited populations (where the drug may have a negative benefit-risk balance for most of the population). Existing labeling approaches fail to do an effective job of communicating to physicians and patients. Especially for patients, better labeling and new communications tools that better put in context the benefits and risks of a new medicine will be important to allow informed decision-making and acceptance of risk. This includes better tools and approaches for effective communication of safety signals (i.e., early indicators of potential safety concerns) that may emerge post-approval, so that physicians and patients can make more informed treatment decisions.

The FDA should improve systems to monitor drugs' risks and benefits in the post-marketing phase. Because innovative drugs may not perform as anticipated once they reach the marketplace, the FDA will be better able to approve innovative products if robust tools are in place that allow regulators and others to detect and manage risks of marketed products. In Chapter 4, we identified the limitations of post-marketing surveillance efforts, and the critical need to scale up and bolster these efforts.

Recommendation 6: Improve FDA's Tools for Monitoring and Communication of Clinical Benefits and Risks

Because knowledge about benefits and risks evolves with experience and over time, FDA requires improved tools to assess and communicate about uncertainty, benefit, and risk.

- (i) FDA should strengthen capabilities for post-marketing surveillance and risk-benefit assessment.** To strengthen post-marketing surveillance, Congress should provide an initial line-item appropriation of \$40 million per year to the FDA to expand post-marketing surveillance capability, such as the Sentinel System, to cover the U.S. population in a rigorous active surveillance and evaluation program to identify and evaluate the potential benefits and risks of medical products and the populations at highest risk for adverse events. The appropriation should increase over time, indexed to the use of electronic medical records in the United States. Additionally, there should be an additional appropriation for a period of several years to build the capacity to perform rigorous studies evaluating real-world safety and effectiveness in clinical care environments. The Federal Government should continue to support efforts, including via public-private partnerships, that advance the science and tools for continuously generating knowledge about the benefits and risks of drugs in the post-marketing phase, for example, through studies using electronic health records.
- (ii) FDA should develop improved systems to communicate risks and benefits of drugs to the public.** The FDA should work with academic researchers, communications experts, patients, prescribers, drug sponsors, payors, and its Risk Communication Advisory Committee to develop and evaluate new tools and approaches for effectively communicating risks and benefits to patients and the public at large.¹⁵⁸ The FDA should also draw on the creativity of the Nation, including through external mechanisms that could administer prize competitions for such tools and approaches.

Improving FDA Management¹⁵⁸

In Chapter 4, we identified a range of management issues at FDA that currently hinder innovation in drug development and evaluation. To address these challenges, we recommend the following reforms:

158. Section 905 of the 2012 FDASIA directs the Secretary of HHS to “implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs.”

Recommendation 7: Reform Management Practices at FDA

The FDA should make the approval process for drugs more clear, predictable, responsive, and efficient, by instituting critical management and communication reforms. The FDA should:

- (i) **For each drug development project, designate a senior scientist to serve as “pre-market review leader.”** This individual would have responsibility for ensuring that sponsors receive clear and timely communication and advice from the Agency throughout the regulatory process, from pre-IND to NDA review and decision. These leaders should have responsibility for providing sponsors with substantive, informal, clear, and timely advice, and for coordinating FDA responses across key areas including toxicology, trial design, manufacturing, and clinical use, and for ensuring timely resolution of outstanding review issues in a timely manner. To accomplish this goal the FDA will need to increase the pool of cross-disciplinary team leaders by increasing division review staff by 25 percent. The FDA should ensure that these leaders have appropriate training and mentorship, as well as appropriate authority, and should create financial and other incentives (perhaps such as special pay authority) to attract and retain the best personnel, including high-level scientific experts across all review divisions. The agency should make every effort to ensure the continuity of pre-market review leaders across the span of the drug application. These efforts should be overseen at a senior level within the FDA. The FDA should also mandate the use of a standard review management system across cross-disciplinary teams, as outlined in the FDA’s Good Review Management Practices guidance.
- (ii) **Establish a Regulatory Innovation Program.** As a science-based agency, FDA must continue to adapt to ever-changing scientific opportunities. To promote innovation within the Agency, the FDA should create a Regulatory Innovation Program to develop and test new scientific, regulatory and management approaches within selected divisions. The Centers’ implementation of such pilots should be overseen at a senior level within the FDA. The FDA should publish regular assessments of the pilot projects and scale up successful pilots.
- (iii) **Widen the use of Special Protocol Assessments.** Special Protocol Assessments (SPAs) have a good track record of providing regulatory predictability in appropriate circumstances. Yet, many observers believe that the receptivity to SPAs varies widely across therapeutic review divisions. The FDA should ensure that all divisions encourage and actively support the consistent use and application of SPAs in appropriate circumstances. Finally, FDA should consider updating its guidance on adaptive trial designs to clarify the circumstances under which adaptive trial designs can be used in SPAs.
- (iv) **Completely overhaul FDA’s IT systems.** The FDA must bring its IT systems up to 21st century standards. The overhaul should develop an integrated platform to manage all drug-regulatory activities, including workload tracking and management, establishment of data management and data aggregation tools, strategies for mobility and connectivity, and appropriate data sharing (both with sponsors and international regulators). FDA should develop and propose

within six months a clear, feasible, and accountable plan to achieve IT modernization. The modernization plan should identify workforce transformation needs, re-balance agency-wide capability initiatives against FDA directorate and FDA center-based initiatives, explore external cloud computing and other transformational approaches to data management, and identify systems architecture needs to greatly reduce the cost and complexity of the technology management lifecycle to ensure long term adaptability.

- (v) Reorganize the internal process for issuing guidance documents and clear current guidance backlog.** The FDA should solicit public input on the most important topics requiring guidance, create a list of high-priority topics, and create an accountable internal process to ensure that guidance documents are completed in a timely manner. This process should include prioritization and timely completion of guidance documents currently under development and currently in draft form. In addition, the FDA should engage third-party organizations with appropriate expertise and credibility (such as the proposed Partnership to Accelerate Therapeutics) to convene stakeholders and develop recommendations for guidance for consideration by the FDA. While such input can facilitate the FDA's process for developing guidance documents, the authority to decide on guidance must remain squarely with the Agency.
- (vi) Improve FDA communication to external community.** To supplement the guidance process, the FDA should create web-based communication tools and a white-paper process to rapidly update sponsors and other stakeholders about policy and technical standards relevant to drug development. FDA should implement a program to improve small business-FDA communications, as recently proposed by the FDA Commissioner.
- (vii) Establish a Commissioner's Advisory Board for Medical Products (CAB).** The FDA currently has a Science Board charged with providing advice and reviewing specific research agendas, programs, and facilities. The FDA Commissioner should establish an external board to provide ongoing advice on the broader topic of the planning, management, and execution of all FDA activities related medical products, including both scientific and other operations. The CAB should include experts and leaders from a range of backgrounds and disciplines, including academia, health care, industry, the investment community, patient advocates, and others. Importantly, the CAB should also include external organizational management experts and should carry out regular reviews of FDA's management and organizational structure. The CAB should be charged with reviewing progress toward implementation of the various reforms discussed in this Recommendation 7 and the implementation of policies to expand Accelerated Approval in Recommendation 3 and 4. High priority should be given to the appointment and performance of pre-market drug review leaders (Recommendation 7(i)) and to improving the consistency of scientific expertise across review divisions.

We recognize these recommendations will have costs, but they are small relative to the FDA budget for drug evaluation and critical to mission of the FDA. The increase could be paid for either by increases in appropriations or increases in user fee support, or a combination. PCAST does not offer an opinion as to the optimal allocation of this support among the sources, but notes that these resources are vital to a robust drug safety and evaluation system.

In addition to the specific reforms recommended above, PCAST notes that the FDA Commissioner has made progress toward increasing the Agency's access to external expertise. We encourage the Agency to continue to evaluate its policies and practices to balance conflicts of interest and ensure transparency, while ensuring FDA staff can regularly interact with external experts particularly on non-product specific scientific and regulatory topics.

D. Economic Incentives

The recommendations above focus on promoting innovation through increasing the probability of success, decreasing the expense, shortening the time, and enhancing the regulatory certainty of drug development. Another potential approach is to increase economic incentives for drug development. Altering economic incentives would require new legislation from Congress.

One of the most powerful incentives is exclusivity periods, which allow sponsors to recover costs and make profits without generic competition. Congress must be careful in defining the use and length of exclusivity periods for several reasons. Exclusion of generic competition results in higher drug prices (which may also be unfairly distributed across generations and society). In addition, exclusivity periods may discourage innovation if designed in a way that makes it more desirable to extend the use of older products rather than develop new, innovative products. Policy decisions about exclusivity periods should balance the benefits of eliciting greater innovative activity against the cost of excluding competition.

The issue is whether and where current economic incentives may be insufficient. There is evidence that this may be the case in some specific areas of great importance to public health. These areas include antibiotics to treat drug-resistant bacteria, prevention interventions for chronic diseases such as Alzheimer's and dementia, and neglected diseases affecting the developing world. In addition, economic incentives may be required to generate knowledge, such as to encourage study of new potential uses of drugs that no longer have patent protection, and to encourage study of some new indications and populations that might benefit from existing drugs on the market. Some have proposed greater use of targeted exclusivity (as has been done for orphan drugs and pediatric indications) as a way to create incentives for these public health needs. Some in the pharmaceutical industry have argued that, more generally, current exclusivity periods are too short and that they need to be extended to encourage innovation and investment. In addition to exclusivity periods, other economics tools have been used or proposed. These include vouchers for priority FDA review, market commitments, and tax credits.

In PCAST's opinion, there is currently insufficient knowledge on which to base wise policy decisions. We need a clearer understanding of the economic impact of current exclusivity periods and the potential benefits and costs of altering exclusivity periods for targeted purposes or in general. In addition, the utility of other tools needs to be better understood. Developing the required understanding requires economic analyses that are beyond the scope of this report and outside PCAST's core expertise. We recommend that the Federal Government commission an appropriate study. The study might best be conducted by the National Research Council.

Recommendation 8: Study Current and Potential Economic Incentives to Promote Innovation in Drug Development

- (i) The Secretary of Health and Human Services should commission a study of economic incentives for promoting investment and innovation in drug development. The study should examine:**
- (ii) The utility of various types of incentives (such as exclusivity periods, voucher for priority review, market commitments, tax credits), including economic analysis of the impact of current and potential incentives on drug developers and on Federal costs;**
- (iii) Whether current incentives promote adequate investment in general and in specific areas of important public health need (such as antibiotics for drug-resistant bacteria, prevention for chronic diseases, and underserved diseases affecting the developing world); and**
- (iv) Whether targeted changes to economic incentives would serve National needs.**

E. Central Role for Patients and Physicians

With respect to all of the recommendations in this report, we wish to emphasize the critical role that patients, consumers, and practicing clinicians must play in discussions of promoting innovation in drug development. Many of the proposals offered in this report will have significant implications for these groups. For example, the public will need to understand and support new regulatory approaches intended to accelerate access to new products, and to know when they are associated with greater risk in early clinical use. Clinicians will increasingly need to ensure that medical products provided expedited market access are used for their labeled indications, and that patients they treat with those products enroll in post-approval studies. For these reasons, it will be essential that patients, patient advocates, consumers, community physicians and other practicing clinicians be meaningfully involved in the refinement and implementation of these recommendations, including through their involvement in the Partnership to Accelerate Therapeutics and in related forums.

F. Timeframe for Action

This report sets out an overarching goal, to be achieved over the next 10-15 years, to “double the current annual output of innovative new medicines for patients with important unmet medical needs, while increasing drug efficacy and safety, through industry, academia and government working together to double the efficiency of drug development by decreasing clinical failure, clinical trial costs, time to market, and regulatory uncertainty.”

Toward this goal, we urge the prompt implementation of the recommendations above. We propose the following timeframe and milestones for implementation:

Within the next year:

Stakeholders launch the Partnership to Accelerate Therapeutics. (Recommendation 2)

FDA takes steps to improve management and communications and to implement new approaches to approval, and Federal support is extended for expanded monitoring of medical products and enhanced communication to the public and prescribers. Specifically, the FDA should launch the Commissioner's Advisory board within one year. (Recommendations 3, 4, 5, 6, and 7)

Within the next three years:

The Partnership will have built active programs to address filling knowledge gaps and business-like clinical trials networks. (Activity stemming from Recommendation 1)

Completion of a study on key economic incentives and levers that should be deployed to support biomedical innovation. (Activity stemming from Recommendation 8)

Within next five years:

FDA should have cleared its backlog of guidances. (Recommendation 7)

A robust safety monitoring system should be full funded and active. (Recommendation 6)

G. Towards a National Innovation Strategy

The scope of this study was limited to actions to advance scientific innovation, reflecting PCAST's expertise. While this report touches upon some aspects of reimbursement policy and economic policy, it has focused primarily on investments in biomedical research, changes in regulatory policy, and bridging of gaps in activity between Federal and non-Federal actors.

We recognize, however, that a national innovation strategy for therapeutics should consider a broader framework, including reimbursement policy, intellectual property, drug manufacturing and supply issues, access to capital for innovators, international trade, competition from other countries, and global harmonization of regulation of medical products. We note that reimbursement policy will have an increasing impact on innovation in drug development, and that it will be important to engage payors in discussions of policy mechanisms, as well as to consider the short and long-term costs to the health care system of such policies.

We recommend that the Administration consider undertaking a broader study of these issues within this larger economic context. Such a study would need to involve White House Councils and Offices and the Department of Health and Human Services (including NIH, FDA, and the Centers for Medicare and Medicaid). It would need to engage patients, regulators, health care payors, physicians, academics, industry leaders, investors, and others.

The continuing development of improved therapeutics is central to advancing public health and is important to our economy. The Federal Government should exercise strong leadership in ensuring that the Nation has a strong ecosystem for drug discovery and development.



Appendix A. Additional Experts Providing Input

Julian Adams

President, Research and Development
Infinity Pharmaceuticals

Jane Axelrad

Associate Director for Policy
Food and Drug Administration

Joshua Benner

President and CEO
RxAnte, Inc.

Jeffrey Brewer

President and Chief Executive Officer
Juvenile Diabetes Research Foundation

Kevin Buchi

Chief Executive Officer
Cephalon

ShaAvhrée Buckman

Director
Office of Translational Sciences
Center for Drug Evaluation and Research

Food and Drug Administration**Anne Claiborne**

Senior Program Officer
Board on Health Sciences Policy
Institute of Medicine of the National Academy of Sciences

R. Alta Charo

Warren P. Knowles Professor, Law and Bioethics
University of Wisconsin at Madison

William Chin

Executive Dean for Research and Bertarelli
Professor of Translational Medicine Science
Harvard Medical School

Louis DeGennaro

Chief Mission Officer
Leukemia & Lymphoma Society

Susan Desmond-Hellman

Chancellor
University of California, San Francisco

Benjamin Ebert

Assistant Professor, Medicine
Harvard Medical School
Brigham and Women's Hospital

Tony Evnin

Partner
Venrock

Margaret A. Hamburg

Commissioner of Food and Drugs
Food and Drug Administration

J. Kevin Judice

Chief Executive Officer &
Chief Scientific Officer
Achaogen

Erin Karnes

Engelberg Center for Health Care Reform
Brookings Institution

Claudia Kawas

Al and Trish Nichols Chair in Clinical
Neuroscience Professor, Neurobiology &
Behavior and Neurology
University of California, Irvine

David A. Kessler

Professor, Pediatrics
Epidemiology and Biostatistics
University of California, San Francisco

REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN
DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

Jonathan Leff

Managing Director, Healthcare
Warburg Pincus

Mark Levin

Co-Founder
Third Rock Ventures

Jack Lewin

CEO
American College of Cardiology

Diane Maloney

Associate Director, Policy Office of Director
Center for Biologics Evaluation and Research
Food and Drug Administration

Elizabeth Mansfield

Director, Personalized Medicine Staff
Office of In Vitro Diagnostic Devices
Center for Devices and Radiological Health
Food and Drug Administration

Mark McClellan

Senior Fellow, Director
Engelberg Center for Health Care Reform
Leonard D. Schaeffer Chair
Health Policy Studies
Brookings Institution

Robert Metcalf

Vice President
Global Regulatory Affairs
Eli Lilly and Company

Karen Midthun

Director
Center for Biologics Evaluation and Research
Food and Drug Administration

Molly Muldoon

Chief of Staff
Office of the Commissioner
Food and Drug Administration

Garry Neil

Corporate Vice President
Corporate Office of Science and Technology
Johnson & Johnson

Steven M. Paul

Director
The Helen and Robert Appel Alzheimer's Disease
Research Institute
Professor, Neuroscience and Psychiatry
Weill Cornell Medical College

Mary Pendergast

President
Pendergast Consulting

Sara Radcliffe

Executive Vice President of Health Section
Biotechnology Industry Organization

Jane Reese-Colbourne

Executive Director
Regan-Udall Foundation

Charles Sawyers

Marie-Josée and Henry R. Kravis Chair in Human
Oncology and Pathogenesis
Memorial Sloan Kettering Hospital
Investigator
Howard Hughes Medical Institute

George A. Scangos

Chief Executive Officer and Member
Board of Directors
Biogen Idec

Lowell E. Schnipper

Chief of Hematology/Oncology
Beth Israel Deaconess Medical Center
Professor
Harvard Medical School

Barry Sickels

Vice President of U.S. Regulatory Affairs
AstraZeneca

APPENDIX A. ADDITIONAL EXPERTS PROVIDING INPUT

Ellen V. Sigal

Chairperson and Founder
Friends of Cancer Research

Lana Skirboll

Vice President
The Zerhouni Group

Marc Tessier-Lavigne

President
The Rockefeller University

Douglas Throckmorton

Deputy Director for Regulatory Programs
Center for Drug and Research
Food and Drug Administration

Steven E. Weinberger

Executive Vice President and Chief Executive
Officer
American College of Physicians

David E. Wheadon

Senior Vice President
Scientific and Regulatory Affairs
Pharmaceutical Research and Manufacturers of
America

Celia M. Witten

Director
Office of Cellular, Tissue, and Gene Therapy,
Center for Biologics Evaluation and Research
Food and Drug Administration

Raymond Woosley

Former President and Chief Executive Officer
Critical Path Institute

Robert A. Yetter

Associate Director for Review Management
Center for Biologics Evaluation and Research
Food and Drug Administration



Appendix B. Acknowledgments

Judith Hautala

IDA Science and Technology Policy Institute

Tom Kalil

Deputy Director for Policy

Office of Science and Technology Policy

Kristen Koopman

IDA Science and Technology Policy Institute

Mary Maxon

Assistant Director for Biological Research

Office of Science and Technology Policy

Sam Thomas

IDA Science and Technology Policy Institute

Gina Walejko

IDA Science and Technology Policy Institute



Appendix C. Acronyms

AIDS	Acquired Immune Deficiency Syndrome
CAN	Cures Acceleration Network
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CTSA	Clinical and Translational Science Awards
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	FDA Amendments Acts
FDAMA	Food and Drug Administration Modernization Act
FY	Fiscal Year
GAO	General Accountability Office
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	Institutional Review Board
IT	Information Technology
NBE	New Biologic Entity
NCATS	National Center for Advancing Translational Sciences
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NME	New Molecular Entity
OMOP	Observational Medical Outcomes Partnership
OS	Overall Survival
PDUFA	Prescription Drug User Fee Act
PFS	Progression Free Survival
REMS	Risk Evaluation and Mitigation Strategies
RUF	Regan-Udall Foundation
SPA	Special Protocol Assessment
SMU	Special Medical Use
TRND	Therapeutics for Rare and Neglected Diseases



President's Council of Advisors
on Science and Technology

www.whitehouse.gov/ostp/pcast