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.

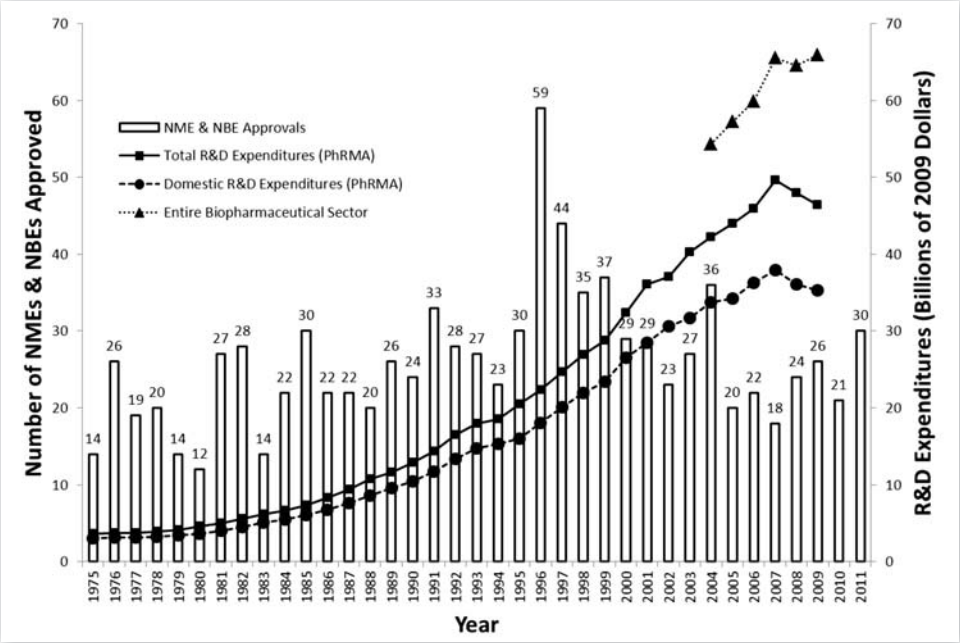
In addition, there is evidence that industry R&D investment, a major component of this innovation ecosystem, is under significant stress:

- 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. Protocols[3] 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.

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.

For a copy of the PCAST report in its entirety, please visit:

http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf