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ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION
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ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH HEARING

21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation

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Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, my name is Sara Radcliffe and I am testifying on behalf of the Biotechnology Industry Organization where I serve as the Executive Vice President for Health. BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO applauds the Committee for its 21st Century Cures initiative to examine what steps the Committee can take to accelerate the pace of cures in America. We are excited to work with you as you seek ways to keep our nation the innovation capital of the world.

I. Introduction

The Challenge of Chronic and Debilitating Disease

The importance of supporting biomedical research and innovation and the development of new therapies cannot be overstated. Today, we face increasing competition around the globe to overtake U.S. world leadership in biomedical innovation. Even in this time of budgetary constraint, it is crucial that we not allow this to happen. We cannot afford to lose the next generation of discoveries that address one of the nation's leading cost drivers – chronic and debilitating disease.

In 2014, the direct costs to American society of caring for those with Alzheimer's will total an estimated $214 billion, including $150 billion in costs to Medicare and Medicaid – the direct cost is projected to reach 1.2 trillion by 2050.[1] By 2030, almost one out of every five Americans – some 72 million people – will be 65 years or older.[2] Clearly, chronic disease increasingly will drive health care costs in the future. Already, almost 84 cents of every health care dollar is spent is to care for

[1] Alzheimer's Association. "2014 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia*, Volume 10, Issue 2 (2014). http://www.alz.org/downloads/Facts_Figures_2014.pdf.
[2] Alzheimer's Association. "2014 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia*, Volume 10, Issue 2 (2014). http://www.alz.org/downloads/Facts_Figures_2014.pdf.

individuals suffering from a chronic disease.[3] It is therefore a national imperative that we find new solutions. This can only be accomplished if we as a nation establish and defend policies that protect intellectual property, promote the effective transfer of new technology, empower regulatory agencies to keep pace with science, encourage the development and adoption of modern approaches to drug development, and continue to invest in scientific research.

The Challenge of Global Competition

We are facing unprecedented global competition to be the world leader in biomedical research. In 2008, China pledged to invest $12 billion in drug development,[4] and in 2011, the Chinese government named biotech one of seven industries that will receive $1.7 trillion in government funding over a five-year period.[5] The European Union's Innovative Medicines Initiative is pumping $2.65 billion into Europe's biopharma industry.[6] America has developed more cures and breakthrough medicines than any other country and is home to over 2,500 biotech companies. However, this is not a position that will be sustained without continued investment and policies focused on supporting and incentivizing the next generation of biomedical discoveries, treatments, and cures. Only by continuing to invest in the biomedical research and development ecosystem will we maintain global leadership, be in a position to increase U.S. jobs, and ensure that all Americans have access to the benefits of biomedical innovation.

The Challenge of Economic and Job Growth

Life science R&D and the biopharmaceutical industry provide high-wage jobs both at public research institutions and in the biotech companies located near centers of academic research. The indirect effects of increased research funding on regional economies are significant. For example, sponsored biomedical research directly generates jobs in the host institutions, and indirect and induced job creation in the region amounts to additional job growth. In fact, the nation's 1.6 million bioscience jobs support an additional 3.4 million jobs in the United States, resulting in a total employment impact of over 5.1 million jobs.[7]

Continuing this pattern of job creation is crucial and will require continued and renewed commitment to forward-thinking policies that will allow this to happen. This clearly is a particular challenge in the current budget climate, but we cannot

[3] Anderson, Gerard. "Chronic Care: Making the Case for Ongoing Care." Robert Wood Johnson Foundation 2010. www.rwjf.org/content/dam/farm/reports/reports/2010/rwjf54583.
[4] Daverman, Richard. "China Launches "Mega Program" to Fund Drug Development." ChinaBio Today. 9 November 2008. http://www.chinabiotoday.com/articles/20081109.
[5] Buckley, Chris. "China to invest US$1.7 trillion over 5 years in "strategic sectors": US official." The China Post. 23 November 2011. http://www.chinapost.com.tw/business/asia-china/2011/11/23/323724/China-to.htm.
[6] Hodgson, John. "€2 billion IMI launched with European pharma." Nature Biotechnology 26, 717-718 (2008).
[7] Battelle Technology Partnership Practice. "Battelle/BIO State Bioscience Industry Development 2012." June 2012. http://www.bio.org/sites/default/files/v3battelle-bio_2012_industry_development.pdf.

afford not to take creative steps to meet that challenge.

II. Discovery

Funding for the National Institutes of Health (NIH)

It is imperative that our country continue to invest in scientific discovery and innovation. Federally supported biomedical research builds the foundation of scientific and clinical knowledge that is widely communicated and used to improve the development of diagnostics, treatments, and cures. The U.S. funds biomedical research primarily through the NIH, the world's premier biomedical research agency; there is no private sector alternative for much of the basic research that NIH supports. However, after nearly a decade of budgets below biomedical inflation, NIH's inflation-adjusted funding is close to 20 percent lower today than in FY 2003.[8] This is a short-term budget-driven approach that is sure to have long-term adverse consequences for all Americans.

Decreasing investment in NIH-supported research will significantly inhibit our nation's ability to make new scientific discoveries that could advance clinical and translational knowledge in how we prevent, diagnose, and treat disease. NIH-supported research also provides training for young researchers. These functions provide the foundation from which scientific findings can be transferred to the private sector. Industry will conduct further research to develop these early-stage discoveries into the next generation of treatments and cures. This collaborative ecosystem benefits all Americans, by producing life-saving and life-altering medical products and also helps create numerous direct jobs in biotech companies as well as indirectly creating jobs within laboratories and other entities that supply such companies.

Ensuring that NIH is well-funded is necessary to sustain the public- private collaboration that transforms biomedical discoveries into innovative treatments for patients.

National Center for Advancing Translational Sciences (NCATS): Opportunity to Engage Industry and other Stakeholders in Finding Solutions to Critical Scientific Barriers[9]

BIO has been actively engaged in conversations with NIH since the concept of creating a new institute focused on translational research was first presented by NIH's Scientific Management Review Board in December 2010. The stated mission of NCATS is "to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions." BIO supports

[8] Federation of American Societies for Experimental Biology. "Budget Cuts Reduce Biomedical Research." http://www.faseb.org/portals/2/PDFs/opa/5.16.13%20NIH%20Funding%20Cuts%202-pager.pdf.

[9] "NIH establishes National Center for Advancing Translational Sciences." NIH Press Release, 23 December 2011. http://www.nih.gov/news/health/dec2011/od-23.htm.

the overarching goal of NCATS and agrees with report language included in the FY 2012 appropriations and statements made by NIH that research initiatives undertaken by NCATS should not be duplicative of the research and development done by industry.

The primary metric for determining the ultimate success of NCATS will be whether its initiatives yield significant reductions in time and expenses in the development of new therapeutics, while expanding the terrain of promising novel targets and pathways, thus improving the delivery of the next generation of medicines to patients. For NCATS to achieve its goal to enhance the development of innovative medicines, it must develop partnerships and collaborations with industry, regulators (including FDA), principal investigators, life science investors, and patient organizations.

In 2012, BIO conducted a survey asking companies to identify research areas that would best serve to improve the process of researching and developing new medicines. The top five recommendations for NCATS research priorities were: identification/validation of biomarkers for predicting therapeutic response, development/validation of novel clinical trial designs, development of predictive preclinical efficacy testing methods/tools; development of predictive preclinical toxicity testing methods/tools and development of effective patient recruitment methods/tools. Success in advancing these research areas would help maintain a robust pipeline of potential breakthrough treatments and cures. Certainly, continued input from industry collaborators will enhance the chance of achieving a salutary outcome.

FDA Funding

Bringing a new drug, biologic, or diagnostic to market requires extensive research, including clinical trials, that may require a decade or more to complete. This risky, long-term investment by biotechnology firms and venture capitalists is predicated on working within an FDA regulatory framework that is predictable, consistent, and well-resourced, and that has the scientific capability necessary to evaluate the benefits and risks of novel products in a timely manner. It is imperative that FDA oversee the development and approval of innovative diagnostics, treatments, vaccines, and cures efficiently.

Nearly 25 cents of every consumer dollar spent in the United States—$1 trillion—is on a product or process regulated by the FDA, and it is critical to American economic health and competitiveness that the agency have the resources necessary to carry out its mission effectively and efficiently. An effective and efficient FDA is critical to encourage biomedical innovation to deliver treatments and cures.

BIO urges that Congress provide $2.784 billion in Budget Authority for FDA for FY 2015. This funding would ensure that FDA programs such as Advancing Regulatory Science, Oversight of Pharmacy Compounding, Supply Chain Traceability, and the Medical Countermeasures Initiative can keep pace with today's science and promote and protect public health. BIO recommends an investment of an additional $100

million in FDA's medical products programs, including a total of $528 million for the human drugs Program and $231 million for the biologics program. In addition, BIO strongly supports legislation that would prevent user fees from being sequestered in future years, as this would threaten FDA's ability to ensure patients get new treatments and cures at the earliest possible time.

III. Development

Leveraging modern advancements in molecular biology and genomics, biotechnology companies have pioneered innovative and life-saving treatments for patients worldwide. New therapeutic and diagnostic products are leading to significant improvements in the care of patients with serious diseases – in many cases providing the first approved treatment for a condition. However, as PCAST and others have noted despite significant investments in the discovery and development of modern therapies and treatments the overall efficiency of biopharmaceutical research and development efforts has been declining steadily for more than 50 years. While many factors have combined to cause this overall decline, it is widely recognized that the increasing timelines and costs associated with clinical trials are key contributors to this problematic trend.

In companion studies published by the Tufts Center for the Study of Drug Development (CSDD) and the U.S. Federal Trade Commission, the average cost of drug development was estimated to be between $802 million[10] and more than $1 billion,[11] respectively, with substantial variation observed by therapeutic category.[12] As a function of increasing development costs, biopharmaceutical R&D efficiency has declined approximately 80-fold over the last 60 years, with the number of new drug approvals per $1 billion spent on R&D decreasing by half approximately every 9 years since 1950.[13] The rising costs of drug development and the resulting decrease in R&D efficiency are complex, multi-factorial problems, but increased cost, complexity, and duration of clinical trials are widely accepted to be important contributing factors.[14,15] Illustrative of this was a study conducted by the Manhattan Institute, which observed that as much as 90% of the development costs for many drugs ultimately approved by FDA were incurred during their phase III clinical trials.[16] Additionally, the duration of the clinical phase of approvals for biopharmaceuticals has steadily increased, from an average of 4.6 years in 1990-

[10] DiMasi J, Hansen R, and Grabowski H (2003) The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*. 22: 151-185.
[11] Adams CP and Brantner VV (2008) Spending on New Drug Development. *Health Economics*. 19, 130-141.
[12] Adams CP and Brantner VV (2006) New Drug Development: Estimating Entry from Human Clinical Trials. *Health Affairs* (2006) March/April, 420-428.
[13] Scannell JW, Blanckley A, Boldon H, and Warrington B (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews: Drug Discovery* 11, 191-200.
[14] Ruffolo RR (2006) Why has R&D productivity declined in the pharmaceutical industry? *Expert Opin. Drug Disc.* 1(2):99-102.
[15] Weatherall M (1982) An end to the search for new drugs? *Nature* 296, 387-390.
[16] Avik R (2012) *The Stifling Cost of Lengthy Clinical Drug Trials*. Manhattan Institute, available at http://www.manhattan-institute.org/pdf/fda_05.pdf .

1994 to an average of 7.1 years in 2005-2009.[17] Concomitant with the increase in clinical trial duration are rising protocol complexities and declining enrollment and retention rates.[18,19]

Confronting the problem of increasing costs and durations of clinical trials is a daunting task. The biotechnology industry is committed to partnering with Congress, FDA, NIH, patients, academia and other stakeholders to make meaningful progress toward improving the conduct of clinical trials. More efficient clinical trials translate to reduced barriers to market for safe, innovative medicines the ultimate goal of patients and industry.

Clinical Trial Modernization Initiative

With this goal in mind, BIO launched its Clinical Trial Modernization Initiative (CTMI) in 2012, based on the pillars of four initial priority issues, which were also highlighted in the PCAST report:

1. *Use of Centralized Institutional Review Boards (IRBs)*

Multicenter clinical trial protocols are most often subject to review by multiple, independent IRBs, which results in delays to study start-up, and inconsistencies in the quality and conduct of ethical review. Centralized IRBs (cIRBs) promote greater efficiency, consistency, and quality of ethical oversight for multicenter clinical trials.

2. *Improving the FDA Qualification Process for Drug Development Tools*

Drug Development Tools (DDTs), including biomarkers, patient reported outcome tools, and novel clinical trial designs, have the potential to improve public health and yield major impacts on the efficiency of drug development programs and their regulatory review. Despite this enormous potential, and a commensurate expenditure of resources, very few DDTs have been successfully qualified. Increasing the efficiency of the FDA qualification process for DDTs could greatly benefit the innovation ecosystem, enabling life–saving therapies to be delivered to patients more expeditiously.

3. *Promotion of Clinical Trial Networks and Partnerships*

Traditionally, in the United States and globally, there has been no established, enduring clinical trials infrastructure. This leads to considerable, unnecessary costs related to study start-up, enrollment, investigator training, and site certification. Advancing efforts by patient advocacy networks, medical centers, health care providers, and other stakeholders to develop clinical trial networks and collaborative partnerships could result ingreater efficiency, consistency, and quality

[17] Tufts Center for the Study of Drug Development (12 April 2010) *PDUFA V Public Meeting.*
[18] Allison M (2012) Reinventing clinical trials. *Nature Biotechnology* 30(1):41-49.
[19] Tufts Center for the Study of Drug Development (2008) Growing protocol design complexity stresses investigators, volunteers. *Impact Report* 10(1).

in the conduct of clinical research and improve the feasibility of clinical trials for special populations.

4. Risk-Based Approaches to Clinical Trial Monitoring

For many pharmaceutical and biotechnology companies, the predominant mechanism to monitor the progress of clinical investigations involves frequent visits to each clinical investigator site to evaluate study conduct and review data for each enrolled subject. Implementation of a risk-based approach to clinical trial monitoring that leverages centralized data monitoring through electronic data capture systems can lead to significant efficiencies for clinical trial sponsors.

BIO is driving change in these priority issue areas by facilitating industry adoption of best-practices, creating strategic partnerships, and advocating for policies to reduce regulatory barriers. We welcome the chance to work with the Committee to advance progress on these important initiatives.

Expansion of Accelerated Approval

Congress has already taken action on several PCAST recommendations through passage of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). For example, PCAST urged FDA to expand the use of the Accelerated Approval pathway beyond the traditional areas of HIV/AIDS and oncology and to be more open to the use of surrogate endpoints and intermediate clinical endpoints that are reasonably likely to predict clinical benefit and can be measured earlier in drug development pending post-market confirmation. FDASIA encourages FDA to utilize the Accelerated Approval program more broadly, which "may result in fewer, smaller, or shorter clinical trials for the intended patient population or targeted subpopulation without compromising or altering the high standards of the FDA for the approval of drugs." BIO is closely tracking Accelerated Approval statistics to understand better how the modernized pathway is being embraced by FDA and which disease areas are benefiting.

While FDA's draft guidance on FDA's Expedited Programs is welcome, we encourage the Agency to clarify further the process for validating a novel endpoint and for FDA and sponsors to discuss potential surrogate or intermediate clinical endpoints earlier in drug development. The PCAST report notes that "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." A lack of process predictability and criteria for developing novel surrogate endpoints can to undermine the program. We will work with FDA to establish clear evidentiary criteria to support the use of a particular surrogate endpoints or biomarkers.

Breakthrough Therapy Designation

FDASIA also established a Breakthrough Therapy Designation process, which has received considerable interest by industry and FDA alike. FDA has designated more than 40 products as "Breakthrough Products" that demonstrate substantial improvements over existing treatments based on early-stage clinical evidence. FDA has approved four of these products to date. By leveraging increased FDA-sponsor coordination and senior, cross-disciplinary involvement to identify the most efficient drug development strategies, drug development times can be reduced substantially. In addition, it is also important that FDA and sponsors work together to reduce non-clinical development bottlenecks, such as scale-up and validation of manufacturing processes, and to ensure timely review of companion diagnostics and combination products.

Timely, Interactive Communication during Drug Development

The PCAST report also states that the "[-D]rug sponsors benefit from clear and frequent communications with the FDA about their specific projects from the earliest stages through final review. 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."[20] Under PDUFA V, FDA committed to a philosophy that timely interactive communication with sponsors during drug development is a core Agency principle. By identifying best practices for FDA-sponsor communication, training reviewers on those practices, and staffing a liaison office to help facilitate FDA-sponsor communication, the agency is taking important steps to improve scientific communication during drug development and reduce unnecessary delays related to miscommunication. The scientific method does not operate in a vacuum, and we encourage FDA to continue to emphasize the importance of interactive scientific discourse during drug development.

Special Medical Use

PCAST, FDA, and other stakeholders have called for the establishment of a "Special Medical Use" pathway to encourage the development of therapies for serious manifestations of more common conditions, such as antibiotic resistant pathogens. We applaud Representatives Gingrey (R-GA) and Green (D-TX) on their work on this issue and stand ready to help articulate a voluntary SMU designation process that can help foster novel drug development while not infringing on the practice of medicine.

Patient Focused Drug Development

The PCAST report notes that "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." BIO fully

[20] PCAST, p. 44

agrees that FDA's drug evaluation process should be appropriately guided by patient perspectives on unmet medical need, the adequacy of existing therapies, anticipated benefits from new treatment options, and tolerance for potential risks.

Under PDUFA V, patient advocates, industry, and FDA have embraced this patient-centric approach to innovative drug development. For example, FDA's new Patient Focused Drug Development (PFDD) program is soliciting views from patient constituencies through meetings on various disease areas to incorporate patient perspectives into regulatory decisions and to help inform future drug development approaches.

The implementation of FDA's new Structured Benefit/Risk framework will also help to ensure that benefits and risks are evaluated the context of unmet medical need and the body of available scientific knowledge so the balance of these factors can be understood more clearly and consistently within FDA and by external stakeholders.

Management Practices at FDA

PCAST's Recommendation #7 is "Reform Management Practices at FDA". BIO has made a number of recommendations in this regard. For example, we have suggested that in addition to stating FDA's critical responsibility to protect the public, the Agency's mission statement should include a clear mandate to encourage the development and advancement of innovative products. This will empower FDA to enhance its capacity commitment to incorporate the latest scientific advances into its decision-making processes.

We have also suggested that an FDA Management Review Board be created to help FDA keep pace with its increasing responsibilities and the latest scientific advances. On a periodic basis and at the request of the FDA Commissioner, the Management Review Board would provide the Commissioner with fresh, visionary, and independent thinking from external experts and FDA thought leaders on how to improve the ability of the Agency to carry out its mission.

We also have suggested that a new position be created at FDA, the Chief Innovation Officer, whose charge would be to ensure that innovative tools and approaches are integrated into FDA review processes, to enhance timely and efficient review and to incentivize the development and utilization of modern scientific approaches to research and development.

IV. Delivery

Post-Market Real-World Data

Advancements in information technology and the adoption of electronic health records places biomedical sciences at the cusp of fully realizing a "learning healthcare system" that can evaluate real-world data to assess the safety and

efficacy of medical interventions, including drugs and biologics, to support the cycle of biomedical innovation. While most randomized, controlled clinical trials can readily identify higher-frequency adverse events and assess clinical efficacy, they must enroll tens of thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. Further increasing the size, length, and complexity of clinical trials is economically unsustainable and places further burdens on the ability of researchers to feasibly enroll and conduct clinical trials.

Rather, we should pursue approaches that more closely integrate reasonably sized pre-market clinical studies with mandatory post-market surveillance and analysis of real-world electronic data to assess safety and efficacy further and to refine the therapy's benefit/risk profile. For example, marketing approval could be granted on the basis of a demonstration of safety and efficacy in a highly targeted patient population (that would require fewer patients in clinical trials) with analysis of electronic health record data and "virtual" clinical studies to support expanded indications in a post-market setting. As part of the Agency's Sentinel Network initiative, FDA has made considerable progress in developing the tools and methodologies for assessing post-market data to identify safety signals; we should continue to build upon that foundation. While the scientific methods in this area continue to evolve, we must embrace a future where we can better leverage real-world data to answer key research questions more efficiently than in large-scale clinical trials.

Reimbursement

While improvements in the discovery and development of medical products are critically important in the bench-to-bedside continuum, patients must be able to access the products or those improvements will be meaningless. Predictable and transparent payment and coverage policies are critical to ensuring that these treatments and cures get to the patients who need them most. As a representative of an industry committed to discovering new cures and ensuring patient access to them, BIO closely monitors changes to how our member's products are covered and paid for. Proposals that limit access to novel medical therapies and technologies can lead to potential delays in obtaining care, or sub-optimal care, resulting in higher health costs and poor health outcomes.

Innovations such as new medical therapies can reduce the burden of, or even cure, costly diseases, as well as keep total societal costs down. However, increasingly we hear from the private investors that fund our smallest companies that reimbursement uncertainty is forcing them to look to alternative investments – not just different companies, but different, unrelated industries, all together. BIO's primary goals are to ensure that patients have access to appropriate therapies and to protect the incentives needed to develop breakthrough medicines to treat the patients of tomorrow. The principles that guide our work in this area are the following:

- Quality: Protect high quality care. Payment reform models must focus on the quality of care delivered, not narrowly on lowering the cost of care.
- Patient Impact: Any proposed payment system reforms must integrate a "patient impact" assessment into their development.
- Access: Protect patient access to appropriate therapies, drug delivery devices, diagnostics and vaccines.
- Adherence: Support patient adherence to therapies.
- Innovation: Maintain incentives to develop breakthrough therapies to address patients' unmet needs and to discover the cures of tomorrow. The research and development of new cures and breakthrough therapies must be a high priority of our nation's health care system – a system that pays for health, wellness and innovation.
- Evidence: Ensure that sound evidence is used for payment policy changes.
- Transparency: Ensure sufficient stakeholder input through a transparent, predictable and inclusive process.
- Adequate Reimbursement: New payment models should not be undertaken without comprehensive evidence that such changes will improve outcomes while lowering overall costs and must place central priority on ensuring access to quality patient care and improving outcomes.

V. Conclusion

BIO appreciates the opportunity to talk with the Committee today, and looks forward to working with you on this important initiative.