

Response from Sara Radcliffe, Executive Vice President for Health, Biotechnology Industry Organization

Attachment 1 Additional Questions for the Record

The Honorable Leonard Lance

- 1. Thank you for your testimony during the May 20 Health Subcommittee hearing on the President's Council of Advisors on Science and Technology Report on Drug Innovation. At the hearing, you testified about the extraordinary expense to bring a new drug, biologic or diagnostic to market and the critical importance of developing and ensuring policies that incentivize investment in the "next generation of biomedical discoveries, treatments and cures." I also agree with BIO's testimony that to ensure investments by venture capitalists, we need an "FDA regulatory framework that is predictable, consistent and well-resourced." The Special Protocol Assessment (SPA) process was created by Congress to create such a framework, and until recently, has promoted innovation and investment in the development of new medicines essential for patient well-being. Do you believe the integrity of the SPA process is essential to ensuring continued investment in biomedical research? If the Agency were to stray from statutory guidance in the SPA decision-making process, what impact would such actions have on the availability of private funding for research and development?***

The Special Protocol Assessment (SPA) process is intended to enhance predictability and consistency to drug development by ensuring that FDA and the Sponsors are in agreement on innovative clinical trials designs and study endpoints for the purpose of regulatory approval prior to initiation of the study. This confidence that FDA will accept the data culminating from these studies plays a role in helping companies attract long-term investment in multi-year clinical trials. However, the value of the SPA process is being publicly called into question.

It can often take several cycles of FDA review to achieve initial agreement on an SPA, which can lead to unnecessary delays in conducting trials. For example, a recent survey of BIO member companies found that 1 in 4 respondents had utilized the SPA process since 2010. However, 78% of SPAs required multiple 45-day review cycles to reach final agreement taking an average of three months to finalize the SPA.

Additionally, recent events have raised concerns about FDA's procedures for adhering to its commitments under an SPA, especially in instances where there may be inconsistent interpretations of the underlying science supporting the SPA. BIO would like to better understand FDA's interpretation of the standard and operating procedures by which FDA would rescind a SPA. Public skepticism about FDA's commitment to SPAs, including in the biotechnology and venture capital communities, could potentially erode the value of the SPA mechanism for drug and biologic sponsors.

The Honorable Gus Bilirakis

- 1. In the world of rare diseases or orphan drugs, there are almost 7,000 diseases affecting about 30 million Americans. Most of these diseases have no treatment. In the last FDA user fee agreement, Congress rewrote the***

statute on Accelerated Approval and directed FDA to expand the Accelerated Approval pathway beyond HIV / AIDS and oncology. The FDA has released guidance on the implementation of this expedited approval pathway. What is BIO's opinion of the guidance that was released? Do you feel confident that accelerated approval is being implemented the way Congress intended?

As part of the *FDA Safety and Innovation Act of 2012*, Congress explicitly encouraged FDA to more effectively utilize FDA's expedited approval pathways — including Breakthrough Therapy Designation and Accelerated Approval — to advance the development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening diseases or conditions.

BIO was pleased to see FDA finalize the draft guidance on *Expedited Programs for Serious Conditions — Drugs and Biologics*. From a procedural perspective, this guidance will help Sponsors to better understand the unique qualifying criteria and features of each expedited program.

The final guidance includes new language to address several high-level issues raised in BIO's comments and those submitted by other stakeholders, such as:

- The importance of employing regulatory flexibility and expedited approval strategies for developing therapies to treat rare diseases (p.2, p. 15, p.21-22)
- The eligibility of vaccines and preventative therapies for expedited programs (p.3)
- Application of Accelerated Approval in acute disease settings (p.15-16.)
- Additional examples of surrogate and intermediate clinical endpoints (p. 18-19)
- Flexibility in manufacturing/CMC as an element of a post-marketing plan (p. 26)
- Discussion of companion diagnostics (p. 27)

We would like to continue to work with the Agency to ensure that these innovative approaches are fully embraced at the review division level across a wide spectrum of serious and life-threatening conditions.

To date, FDA has granted more than fifty requests for Breakthrough Therapy Designation in areas such as oncology (27%), hematology (19%), infectious disease (23%), and rare conditions.^{1, 2} To date, FDA has reviewed and approved six Breakthrough designated products to treat cystic fibrosis, leukemia, lymphoma, hepatitis C, and lung cancer — many in record time after only 4-6 months.³ However, it is unclear whether this program is being met with the same level of interest across all FDA centers and review divisions as is the case in the oncology and anti-infective review divisions.

FDASIA also expanded and modernized FDA's existing Accelerated Approval pathway, which can grant approval to a therapy for a serious or life-threatening disease on the basis of a surrogate or intermediate clinical endpoint that can be measured earlier in drug

¹ Biotechnology Industry Organization (BIO), *Breakthrough Therapy Designation and Approvals*, updated June 2, 2014

²FDA, Dr. John Jenkins, Director, Office of New Drugs, CDER, *CDER New Drug Review: 2013 Update*, December 11, 2013, <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM378227.pdf>

³ FDA, *Breakthrough Therapy Approvals*, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373418.htm>

development. This may result in fewer, smaller, or shorter clinical trials for the intended patient population and can allow patient access to life-saving therapies years earlier than traditional approval.⁴ FDASIA provides FDA with additional flexibility to accept novel study endpoints and employ the pathway in therapeutic areas beyond the traditional scope of HIV/AIDS and oncology. Since enactment of FDASIA, at least seven products to treat serious diseases have been approved under Accelerated Approval, including five in oncology, one in infectious disease, and one for the central nervous system. Given the limited number of approvals under the program and the multi-year drug development timelines, it is premature to assess whether the program is having its intended effect.

While FDA's procedural guidance is welcome, we have requested that the Agency clarify further the criteria for validating a novel endpoint for Accelerated Approval and the process for engaging FDA in that discussion earlier in drug development. For example, the guidance states that "determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment" and that "this guidance does not, however, address the specific clinical evidence needed to support a conclusion that a particular surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit or IMM because such evidence is case-specific and is not readily generalizable."

The 2012 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." Indeed, a lack of process predictability and criteria for developing novel surrogate endpoints can potentially undermine the intent of the Accelerated Approval program.

2. One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract?

Please see our response on SPAs above.

3. For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate endpoints that are reasonably likely to predict a clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can FDA work with stakeholders to determine new endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?

As discussed above, BIO believes that FDA's process around the utilization and acceptance of surrogate and intermediate clinical endpoints has been variable across review divisions. We look forward to working with the agency to establish clear lines of communication on discussing an endpoint to support Accelerated Approval early in development, and also evidentiary criteria for supporting that endpoint.

⁴ Johnson, Ning, Farrell, Justice, Keegan, Pazdur, *Accelerated Approval of Oncology Products: the Food and Drug Administration Experience*, Journal of the National Cancer Institute, February 7, 2011, <http://jnci.oxfordjournals.org/content/103/8/636.short>

FDA has been open to working with private-public partnerships and consortium to research new biomarkers and potentially new surrogate endpoints. However, to date progress in validating or qualifying these measures for regulatory purposes has been slow to produce new drug development tools that can improve the efficiency of drug development. For instance, since 2008 only three biomarkers have been successfully FDA-qualified, while scores of other potential biomarkers that are being developed by consortia are mired in the FDA consultation phase in order to clarify the context of use and determine the level of evidence need for qualification.

4. What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?

Advancements in information technology and the adoption of electronic health records place biomedical sciences at the cusp of fully realizing a “learning healthcare system.” Such a system 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 from drug discovery and development to the point of healthcare decision-making. However, additional research and methodology development is needed to validate the use of real-world evidence to support claims of safety and efficacy.

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 to also consider efficacy endpoints. While the scientific methods in this area continue to evolve — and are evolving in particular through the Reagan-Udall Foundation’s Innovation in Medical Evidence Development and Surveillance (IMEDS) program — we must embrace a future where FDA and industry can be aligned to better leverage real-world data to answer key research questions more efficiently than in large-scale randomized clinical trials.

Enabling the appropriate use of rapidly growing digital health information can help not only to inform regulatory approval and fulfilling post-approval commitments, but also in providing relevant information at the point of healthcare decision-making. Crucial to this effort will be broadening access to existing federal data resources — such as from Centers for Medicare and Medicaid Services (CMS)-administered federal healthcare programs, the National Institutes of Health (NIH), and the Centers for Disease Control and Prevention — and standardizing the collection of these data across various sites of care to provide a comprehensive, continuous picture of an individual’s health and the care he/she receives.

5. Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leveraged for supplemental applications?

Continued technological advances in gathering and employing data have the potential to improve the timeliness of drug development. For example, while randomized, controlled clinical trials (RCTs) are considered to be the gold standard to assess safety and clinical efficacy, they often evaluate uniform populations remotely connected to the use of drugs in regular clinical practice or in settings reflecting real-world health care delivery. RCTs can

readily identify higher-frequency adverse events and assess clinical efficacy, but they must enroll thousands of patients to be powered sufficiently to detect rare adverse events or slowly progressing clinical manifestations. Yet increasing the size, length, and complexity of clinical trials is not an economically sustainable option and places further burdens on the ability of researchers to enroll and conduct clinical trials feasibly.

Rather, we should pursue approaches that more closely integrate reasonably sized pre-market clinical studies and real-world data with mandatory post-market surveillance and analysis of additional real-world data to assess safety and efficacy further and to refine the therapy's benefit/risk profile. For example, marketing approval should 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 in a post-market setting to support expanded indications.

6. As a Member of Congress, we hear tales about how companies meet with FDA on drug approval, and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science?

The scientific method does not operate in a vacuum, and it is critical to promote the appropriate exchange of ideas and scientific learnings between academia, the private sector, and government. During drug development, sponsors often have difficulty communicating with their FDA review divisions outside of written exchanges of letters or formally scheduled meetings. Informal scientific dialogue can play an important role in understanding FDA expectations and ensuring that medical officers are aware of the underlying science supporting an investigational product.

Further, sequestration and recent budgetary restrictions have prevented FDA medical officers from attending scientific conferences and technical meetings. This has hindered the Agency's ability to keep pace with the rapid advancements in basic and applied research. We ask Congress to ensure that the Agency has adequate funding for professional development activities, scientific and technical capacity building, and scientific leadership.

The Honorable Jan Schakowsky

1. A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new Hepatitis C dn1g treatment costs about \$100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation?

As a representative of the leaders in the biopharmaceutical space, BIO is focused on policies that enhance the development of lifesaving treatments and cures, and ensuring patient access to them. Due to the expansions in the Affordable Care Act (ACA), more patients have the insurance they need to help them access care. Unfortunately, those benefits are increasingly characterized by narrow provider networks and higher cost sharing that undermines the very mission those insurance expansions were intended to meet. That's why biopharmaceutical innovators provide or support patient assistance programs to help patients gain access to needed therapies, either when they are uninsured or when their

insurance coverage has fallen short of their needs. Allowing innovators to continue to offer these programs is a critical component of ensuring patient access where insurance has fallen short.

- 2. I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIH is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?***

Basic research begins and underpins the process of discovery. The importance of having a sustained federal commitment to funding basic research cannot be overstated. 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 federal government funds biomedical research in the United States primarily through the NIH. The NIH is the nation's premier biomedical research agency and there is no private sector alternative for much of the basic research that NIH supports. NIH-supported research advances our knowledge about diseases and paves the way for the biopharmaceutical industry to develop the next generation of medicine therapies. 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. Decreasing investments in biomedical research will have long-term impacts, because making scientific discoveries and developing those discoveries into treatments and therapies that will improve the lives of patients is a long and difficult process that requires sustained commitment and investment.

This collaborative ecosystem also serves to create numerous direct jobs within the companies themselves as well as the indirect job creation with the numerous laboratories and suppliers contracted by the companies. As Alexis Borisy, Partner, ThirdRock Ventures, a leading investor in disruptive early stage companies, stated during his testimony before the Energy and Commerce Health Subcommittee on June 11th:

"Research dollars provided by the National Institutes of Health to universities and colleges throughout the country also serve to train future scientists for 21st century jobs. Currently, the U.S. biomedical research sector supports over 5 million high-paying jobs in the United States and has tremendous potential for growth. However, we must understand that our position as the global leader in medical science is constantly being challenged, and without a sustained commitment for scientific discovery, this is not a position that will be maintained."

Congress must focus on how to increase the NIH budget appropriately on an annual basis. Without such an annual increase, the budget and NIH's ability to fund meritorious research effectively and at a level that advances innovation declines with the inevitable increases in the cost of research. Ensuring that NIH is well-funded is necessary to sustain the public-

private collaboration that is transforming biomedical discoveries into innovative treatments for patients. Furthermore, efficiencies in NIH processes could lead to cost savings.

Consideration also could be given to how public-private partnerships might help. Increasing private funding for government-sponsored basic and applied research would require discussion of how to incentivize such funding and how such funding would be administered. It would be important, for any such funding from for-profit sources, to determine how a system could be structured to prevent either the appearance of or actual conflict of interest.

The Honorable H. Morgan Griffith

1. *What legal barriers currently exist that limit the potential for doctors, researchers and drug companies to communicate on how therapies are working for patients in the real world? What can we do to break down some of those legal barriers that are preventing reasonable and valuable treatments from getting to patients?*

Broadly, FDA interpretation of current law and regulation limits a manufacturer's proactive communication about its product. Specifically, proactive manufacturer communication is generally restricted by FDA only to the information contained in the product label. The labeling includes the product indications for use approved by FDA, and product labeling is prohibited from listing any use that has not been approved by FDA. The FDA, of course, does not regulate the practice of medicine, and once a product is introduced, medical practice begins its iterative process, and scientific experience and knowledge may outpace the approved product labeling. Off label uses of biopharmaceutical products, based on practitioner real world experience with a product, are common, and recognized as having a societal benefit.

Nonetheless, proactive communication by a manufacturer of information about the use of a product that is not contained in the product label may be viewed as "off label promotion," and subject to significant enforcement efforts. This limitation affects even communication by a manufacturer of truthful and not misleading medical or scientific information with practitioners about the real world use of manufacturers' products. Manufacturers may not share information and participate in the iterative scientific and medical dialogue about their products on a proactive basis, instead only being permitted to do so reactively with various interpretive FDA restraints. Such approaches hinder the various users of medicines from easy access to information that can help them understand the range of treatment options for various conditions and impede the most effective use of certain medicines.

In addition, current law deals with the important question of providing payers and others with meaningful information regarding the pharmacoeconomic benefits of medicines. Specifically, Section 114 of the *Food and Drug Administration Modernization Act of 1997* (FDAMA) permits communication of pharmacoeconomic information to formulary committees and similar entities only if the information is directly related to an approved indication. This has undermined innovators' ability to meet requests for such information, which is increasingly demanded if our healthcare system is to evolve to one based on patient-centered outcomes and "value".

Broadly, the provision of truthful and non-misleading information to providers, payers, and patients about real world evidence and uses should not be impeded by unnecessary and cumbersome regulatory restrictions or requirements.