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BY E-MAIL

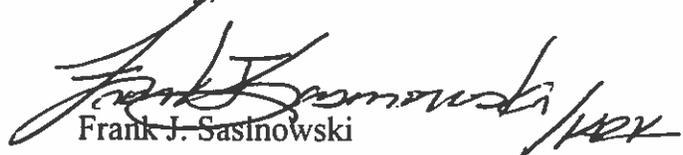
Sydne Harwick
Sydne.Harwick@mail.house.gov

Dear Ms. Harwick:

I have provided responses to the questions for the record provided by the Members of the Energy and Commerce Subcommittee on Health regarding my testimony for the hearing entitled, "21st Century Cures: The President's Council of Advisors on Science and Technology (PCAST) Report on Drug Innovation" held on Tuesday, May 20, 2014.

Please let me know if you have any questions or concerns related to the responses I am submitting.

Sincerely,



Frank J. Sasinowski

Director
Hyman, Phelps & McNamara, P.C.

Director
National Organization of Rare Disorders

The Honorable Gus Bilirakis

1. 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?

Yes, in the context of orphan drug development for rare diseases, SPA agreements have allowed the FDA and Sponsors to discuss and gain concurrence prospectively on protocol design and statistical issues, which has yielded greater certainty in drug development. Successful clinical trials for Americans with rare diseases have resulted from SPA agreements in which FDA has demonstrated considerable flexibility in clinical trial design, including subjects to be enrolled, selection of endpoints, duration of trial and safety information to be collected.

2. 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?

From my observations, FDA works closely with both Academic and Industry Sponsors to determine appropriate new surrogate endpoints, such as seen in FDA's collaboration with the Critical Path Institute and its Industry partners on new surrogates. Furthermore, FDA has provided additional guidance to sponsors in its recently released final guidance, titled, "Expedited Programs for Serious Conditions – Drugs and Biologics." Section VII.C. of the guidance, titled "Evidentiary Criteria for Accelerated Approval," describes several factors FDA weighs in assessing whether the available evidence is sufficient to allow the Agency to conclude the proposed surrogate endpoint is reasonably likely to predict clinical benefit. In an analysis I conducted along with my colleague Alexander Varond, in which we looked at each of the 19 Subpart H approvals (that are not for AIDS or cancer), we found that FDA has shown great flexibility in applying its Accelerated Approval standards to therapies for serious diseases under FDA's review. *See* Comment of Hyman, Phelps & McNamara, P.C., Docket No. FDA-2013-D-0575 (Aug. 26, 2013), available at <http://www.hpm.com/pdf/blog/Subpart%20H%20Analysis%20-%20FDA-2013-D-0575.pdf>.

3. 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?

No comment. I am not an expert in post-approval outcomes data.

4. 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?

There are benefits as well as limitations in using real world data in supplemental applications. In particular, when the real world data mirrors the already approved dosage in a similar population (e.g., gender, age, health status), then the observed safety outcomes can be useful in providing information that may confirm the safety profile of the drug as it is known for the approved indication or use. However, with regard to establishing evidence of efficacy, real world data will often lack sufficient methodological rigor to be of great value in advancing our understanding of the effectiveness of therapy (see 21 C.F.R. 314.126, the regulation that describes the conditions needed to have an adequate and controlled study). If, however, by “real world,” the question is referring to studies that would be considered adequate and well controlled but just not conducted pursuant to a commercial Sponsor’s investigational new drug (IND) exemption, then such “real world” data may be leveraged for both supporting the safety and effectiveness of the drug for the new use in a supplemental application. I have been involved with a number of instances, including one in which a patient advocacy organization, the LAM Foundation, had a major hand in designing and analyzing a study of an already approved drug, sirolimus, for another use: to treat women with LAM. This was a rigorous trial and its results were published in the *New England Journal of Medicine* and touted by the editors of the journal as a shining example of a patient organization leveraging an existing approved drug for a new use. See Francis McCormack et al., *Efficacy and Safety of Sirolimus in Lymphangiomyomatosis*, 364 *N. Engl. J. Med.* 1595 (2011); see also Julie Ingelfinder & Jeffrey Drazen, *Patient Organizations and Research on Rare Diseases*, 364 *N. Engl. J. Med.* 1670 (2011).

5. 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?

Ensuring that FDA review staff are knowledgeable about the latest science is very important. From my experience in the rare disease space, it is not uncommon that FDA may not have an in-house medical reviewer with expertise in a particular rare disease or maybe who has ever even seen a patient with a particular rare condition since such conditions may be very rare. In these situations, Sponsors will often bring a rare disease medical expert to meet with the FDA, making them available to FDA to answer questions from their experience. Additionally, FDA will consult directly with rare disease medical experts and rare disease patient advocates to get input on complex issues, such as the risks and benefits of potential therapies, the design of clinical trials, and medical needs not met by existing therapies. NORD has been a proponent of this type of expert consultation, and along with the Cystic Fibrosis Foundation, was a champion of the Expanding and Promoting Expertise in Review of Rare Treatments (EXPERT) Act that was included in the Food and Drug Administration Safety and Innovation Act (FDASIA), which reinforces and expands FDA access to rare disease experts.

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 drug 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?

While I am not an expert in drug reimbursement, programs such as NORD's Patient Assistance Programs provide financial assistance with insurance premiums and co-pay fees, as well as assistance with reasonable and appropriate diagnostic testing expenses and travel to and consultation with disease specialists that are not covered by a patient's insurance plan. NORD also hosts a number of medication- and disease-specific assistance programs. See NORD's Patient Assistance Programs, *available at* <https://www.rarediseases.org/patients-and-families/patient-assistance>. This type of program, run by a non-profit patient advocacy organization, provides a trusted, neutral venue for patients with financial need to gain assistance. Unfortunately, NORD has been told by Sponsors that for-profit companies may be setting-up and operating shell so-called "non-profit" organizations to benefit from the operating revenue of Patient Assistance Programs. This siphons money from legitimate patient advocacy organizations that use Patient Advocacy Programs as a way to help patients and generate

much needed operating revenue. Meanwhile, these third-party operated programs do not provide the comfort of neutrality and reassurance that the program is operating in the best interest of the patient, which is crucial to protect vulnerable patients in need of assistance. The Subcommittee can provide leadership in further defining legitimate patient advocacy and other non-profit advocacy organizations to prevent this perversion of the system. The Subcommittee can also provide authorization for funding, as well as provide support for sponsor funding, to qualified patient advocacy organizations to host Patient Assistance Programs.

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 NIFI 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?

Thank you for your important testimony. Your testimony makes clear the harm caused by inadequately funding the NIH. I hope that we can work together to ensure that NIH has the resources it needs to ensure that we remain the world's leader in innovation and that we accelerate our ability to discover new treatments and cures that save lives and improve health.

I concur, and NORD has advocated, that the National Institutes of Health (NIH)'s funding for basic research, as well as translational research, has helped facilitate the development of new, innovative therapies for patients. I would not disagree that a reduction in inflation-adjusted funding would be a detriment to our biomedical research capacity. I would like to mention the need for increased appropriations for the Orphan Products Grants Program administered by the FDA Office of Orphan Products Development. This federally funded program provides grants to academic researchers and industry for pivotal clinical trials on new orphan drugs, medical devices, and medical foods for rare diseases. The Orphan Products Grants Program began in 1983 with a modest appropriation of \$500,000 and has seen increases in the appropriation to the current \$14-15 million (even though its authorization is for up to \$25 million). Funding for this has remained constant at that level since 2005 with a decrease as a result of sequestration.

When inflation is taken into account, the program has actually only risen to about \$6 million in 1982 dollars. Despite the relatively low levels of funding, the program has truly made a difference in the lives of patients, with about 10% of all therapies approved by FDA for Americans with rare diseases have received funding by the Orphan Products Grants Program. Given the extremely modest funds provided by taxpayers to this program, this return on taxpayers' investment (ROI) is highly remarkable! While FDASIA reauthorized grant funding for the Orphan Products Grants Program, increasing future funding will allow additional studies in conditions in vulnerable and difficult-to-treat populations, as well as those that have no available options.

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 the patients?

At the May 20th hearing, I stated that I was (and still am) unaware of what state and federal legal barriers may exist that impede the conduct of natural history studies and patient registries, but I repeat here how critical it is for developing new innovative therapies for Americans with rare diseases that our legal systems not slow or halt natural history studies and patient registries. Patient registries are a cost-effective instrument for increasing knowledge of a disease, for supporting fundamental clinical and epidemiological research, and for conducting post-marketing surveillance of drugs. Natural history studies are an important tool for understanding the etiology of a disease, its range of phenotypic manifestations, and its relative rate of progression, all of which can support identification of biomarkers and surrogates as well as innovative study design, which collectively advance drug development. As I mentioned in my remarks at the hearing, if we understand more about the natural history or progression of a disease, we will be better able to discern what is the treatment benefit of a novel therapy versus what is the natural course of the disease. Similarly, we could tell what is a safety signal that is due to the therapy rather than a signal that is part of the natural course of the progression of the disease. Therefore, encouraging the development of natural history studies and patient registries in every disease is very important. Congressional support for these critical tools would be vital to securing the aid of medical professionals and institutions in gathering information in a consistent, uniform manner and sharing such information for the benefit of patients and drug development.