

July 18, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
House Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts:

Thank you again for the opportunity to testify before the Subcommittee on Health on the “21st Century Cures: Examining the Role of Incentive in Advancing Treatments and Cures for Patients.” As a follow up to your request, below are my responses to the questions asked by several members of the committee.

The Honorable Joseph R. Pitts

1. The size and cost of clinical trials is an impediment to investment and innovation, particularly for products treating diseases that impact large patient populations. How can advances in technology make trials more efficient?

There are advances in technology on multiple fronts that could serve to improve how we can more efficiently and effectively conduct clinical trials. In the 21st century we must move away from the more for more’s sake mentality to a philosophy that considers what is actually informative. It is also important to understand that we have already moved into a life-cycle approach to drug development that includes many post-approval monitoring and data collection activities that have not yet been integrated to how we develop, review and approve new medicines. I will briefly discuss 3 areas where modern technologies could serve to improve the development and approval processes.

Improving FDA Acceptance of Modern Drug Development Tools

As I discussed in my testimony the ability to utilize modern drug development tools such as biomarkers, patient reported outcomes, and novel clinical trial designs is inconsistent across review divisions. While we have seen significant progress for drugs that treat oncology and rare diseases, we have not seen the same progress in the utilization of modern approaches for chronic and progressive diseases. In the absence of concentrated efforts by regulators to communicate how, when and on what basis modern approaches will be accepted the regulatory process will continue to lag behind modern science. The question is not always what technology is available but rather will the technology that is available be able to be utilized during the regulatory process.

This issue must be addressed in both a prospective and retrospective manner. On the prospective side there should be a process for sponsors to interact with FDA early in the clinical development process to discuss the use of novel tools and approaches in a clinical development program. Any process should ensure that industry, FDA, and any appropriate external medical experts or patient voices necessary to ensure a fully informed discussion are incorporated into the process. On the retrospective side there needs to be a more consistent and transparent process whereby FDA evaluates biomarkers and modern approaches that are novel or have

been utilized for approval of rare diseases or drugs that treat serious and life-threatening diseases are evaluated via a public commenting process and present ideas on how those tools could be employed in other disease areas to the public. This type of process should also be forward leaning and allow for input regarding modern approaches that are being developed and studied by NIH and other public private partnerships. It is imperative that these activities do not end with a report but rather lead to activities such as adaptive/Bayesian clinical trial methodology development, pilot programs and new guidance. And finally, it is critical that there is a concentrated effort to assess, evaluate and communicate how these approaches could be utilized for drugs that are designed to treat large patient populations.

FDA, should also be looking to work with NIH and public-private partnerships to pilot and establish guidelines for the use of modern tools such as the utilization of smart phones that could improve the ability of sponsors to more effectively obtain patient reported outcomes.

Use of 'Big Data' and Post-Market Real-World Data

The other technological advancement is the ability to collect data from multiple sources. It would be beneficial for Congress to encourage or authorize FDA to accept data from non-traditional sources such as historical data, data from electronic health records, claims databases, registries or other sources to support clinical development activities. We should also consider how these databases could be utilized to empower more effective and efficient clinical development and approval of new medicines. This could include approaches that allow for more reasonably sized pre-market clinical studies on safety and effectiveness with mandatory post-market real-world data collection and analysis to assess the safety and efficacy further in the real-world. Enabling the use of rapidly growing digital health information could greatly advance how we develop new medicines and would serve to attract investment in more disease areas such as cardiology, endocrinology and progressive/chronic neurological diseases.

Adaptive and Expedited Approval Pathways

We have already discussed biomarkers and novel clinical trial designs and their potential to modernize clinical development. We are also making advancements in the ability to develop and utilize diagnostics to identify targeted subpopulations of patients. Improving the process by which FDA approves the utilization of companion diagnostics in drug development could significantly improve the industry's ability to develop medicines for diseases that treat chronic and progressive diseases where there are varying risk-benefit profiles within each disease or where there are genetic markers that may be predictive of how patients may respond to treatments.

There are also adaptive and expedited approval pathways currently being discussed that could enable more investment in and development of medicines for diseases that affect large and diverse patient populations. These include ideas such as Special Medical Use and Adaptive Licensing. The idea is to allow for a prospective clinical development program that is designed to initially evaluate, test and approve a medicine for a subpopulation of patients. The industry sponsor can then conduct subsequent clinical trials to evaluate, test and approve that same medicine for a broader patient population. The European Medical Agency (EMA) is currently conducting a pilot program with selected companies to explore how adaptive licensing can be developed for specific medicines. If authorized in the United States, these types of programs would serve to incentivize investment for drugs designed to treat chronic/progressive diseases.

- 2. Understanding that lengthy clinical trials with a large number of participants are currently the norm for drugs treating chronic diseases such as heart diseases and stroke, what processes does FDA in place to provide the necessary certainty to sponsors up front so that, when resources are devoted to drug-development in these areas, investors and companies can plan accordingly? [Please see response to Question 1.]**

In addition to the comments made above, your question as to sponsor confidence in clinical trial development and evaluation by the FDA is not consistent across FDA review divisions. While there have been improvements since passage of FDASIA there is still a need to encourage more scientific dialogue between FDA and sponsors throughout the development process. There are tools such as Special Protocol Assessments (SPA) that are intended to address the issues you raised however these are not used by a majority of sponsors and those that do utilize them often have to undergo a lengthy process to obtain a SPA and does not always offer guarantees that the agreement will be upheld. Thus, many companies make the determination that the value versus the burden leads to a decision to forego utilization of a SPA. That said, in all cases, more scientific interaction with FDA review teams and review divisions should be encouraged to ensure that each drug development team is communicating with the sponsor, external experts as needed and patients as appropriate to ensure that the program is being tested and evaluated in a manner that is reflective of current science, current technologies, and takes into account the disease and patient being treated.

The Honorable Michael C. Burgess

- 1. Would you comment on some of the barriers that Class III medical device manufacturers face when seeking coverage and payment from CMS for innovative cutting edge technology that improves the lives of patients?**

Securing coverage and payment for Class III medical devices is a very complex and unpredictable process and can add an additional three to five years more before patients can benefit from a new product. Each phase of reimbursement process has its own set of challenges. One of the biggest challenges companies face is the data requirements payors (both government and private) impose before granting coverage because the requirements are often unclear and so high. Also, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it, while physicians and hospitals will not agree to use the product unless they get paid. Equally challenging is that data and utilization requirements are very ambiguous. There is also increasing evidence that payors are raising the standard for coverage determinations.

The Honorable Cathy McMorris Rodgers

- 1. Your testimony specially references the length of clinical trials as being an impediment to investment. What are some specific ideas on what we could do to streamline the way trials are conducted? How would this affect investment in the bio-pharma space? Please see response to The Honorable Joseph R. Pitts Question 1.**

2. How can we improve our existing research structure in a way which incentivizes more investment? What is the possibility for clinical trial networks? Or more partnerships with NIH? How about interaction of the SBIR/STTR program with NIH?

I serve on BIO's Emerging Companies Section Governing Board. Recently, Reps. Jim Gerlach (R-PA), Richard Neal (D-MA), Mike Kelly (R-PA), and Ron Kind (D-WI) introduced H.R. 4855, the Partnerships to Advance Revolutionary Technology and Novel Entrepreneurial Research (PARTNER) Act. This bill would allow small companies to partner with their investors on a research project and share the tax assets (net operating losses and R&D credits) generated by the R&D that could substantially incentivize investment in the early-stage and clinical development in the biopharmaceutical industry.

It could also be worthwhile to examine current public-private partnerships and examine ideas for creating incentives for increased private sector funding in such endeavors. Partnerships including pre-competitive information sharing among NIH, FDA, academia and industry as well as partnership among medical product developers have and could yield enormous benefits. These types of partnerships can work together to tackle issues such as finding solutions to critical scientific barrier questions and the collection and analysis of things like natural history studies data. All of which can serve to de-risk clinical development and thus make investment more attractive. NIH could also serve a critical role in working with FDA and industry to evaluate, test and validate new approaches to clinical trial development (ex. adaptive clinical trial designs, novel endpoints etc.). Improving the regulatory process for clinical development would serve to incentivize investment in the development of new medicines.

The NIH SBIR/STTR program serves a critical role in providing funding for early-stage proof of concept studies. This program serves to advance research projects to the point where it can attract venture capital. This program has been very successful. However, the investment environment for early-stage research is still a difficult one. As I mentioned in my testimony first-time financings are down 35% from 2008. It may be worthwhile for Congress to consider creating tax incentives for investment in early stage research projects.

Establishing a stable and enduring clinical network infrastructure in the U.S. could considerably reduce costs associated with the start-up, enrollment, investigator training, and site certification for clinical trials. There are currently some clinical trial networks in place such as the Cancer Cooperative Groups funded by the National Cancer Institute. Congress could authorize the establishment of such groups, with consultation between NIH and FDA with funding from government sources and/or public-private partnerships or on a fee-for-service basis.

3. You mention the need for FDA to allow for the utilization of modern tools- such as biomarkers and personalized medicine to diagnostically define subsets of a disease. Do you think the FDA and its current regulatory framework is equipped to approve these types of products? Do you think there are adequate incentives in the market for these types of innovative diagnostics?

The current regulatory process for acceptance of modern tools and approaches to clinical development remains inconsistent across review divisions. There appears to be a much stronger willingness to accept modern tools, novel endpoints and flexible clinical trial designs in the oncology and rare disease space but reluctance in other disease areas especially for drugs designed to treat chronic/progressive diseases. Additionally, the criteria by which FDA will

accept novel tools and approaches is often not clearly understood by investors or the industry. As discussed under Question 1, it would be beneficial if the FDA and industry sponsor could interact with FDA early in the clinical development process to discuss the use of novel tools and approaches in a clinical development program. Any process should ensure that industry, FDA, and any appropriate external medical experts or patient voices necessary to ensure a fully informed discussion are incorporated into the process. Additionally, there needs to be a more consistent and transparent process whereby FDA evaluates biomarkers and modern approaches that are novel or have been utilized for approval of rare diseases or drugs that treat serious and life-threatening diseases are evaluated via a public commenting process and present ideas on how those tools could be employed in other disease areas to the public. This type of process should also be forward leaning and allow for input regarding modern approaches that are being developed and studied by NIH and other public private partnerships. It is imperative that these activities do not end with a report but rather lead to activities such as adaptive/Bayesian clinical trial methodology development, pilot programs and new guidance. And finally, it is critical that there is a concentrated effort to assess, evaluate and communicate how these approaches could be utilized for drugs that are designed to treat large patient populations.

There are not, currently, enough incentives to fund activities for the identification of new biomarkers, to develop evidence supporting the utilization of current biomarkers, to develop and conduct novel clinical trials designs or to develop novel diagnostics. The development of novel diagnostics has barriers on multiple fronts.

First, the regulatory process for the inclusion of diagnostics in drug development is often burdensome and communication between review divisions and centers can often be inconsistent and/or cause delays in the clinical programs. One element of the Breakthrough Therapy Designation program is to integrate and coordinate cross-disciplinary review staff early, often and throughout the clinical development program. These activities could be monitored and utilized to establish best practices for how to more effectively review companion diagnostics in general.

Second, reimbursement for diagnostics, while improved after passage of the *Improving Medicare Policies for Clinical Diagnostic Laboratory Tests* in 2014, it is still considered a negative factor when considering whether to invest in the development of novel diagnostics. In my testimony I proposed that the Committee consider a process whereby CMS create a program for diseases important to the public health with high unmet diagnostic needs (ex. Alzheimer's and diabetes) and establish a payment policy for some meaningful determined period of time that would incentivize investment in and development of novel diagnostics for these critical diseases.

Clear payment policies of personalize medicine tools and modern regulatory approaches would advance personalized medicine by leaps and bounds.

The Honorable Gus Bilirakis

- 1. Your testimony mentioned that FDA allows for the use of novel endpoints, biomarkers and non-traditional clinical trial designs, but lacks transparency and consistency in their approach. How could we improve the process and encourage regulatory to use every tool in their proverbial toolbox? Please see response to The Honorable Joseph R. Pitts Question 1.**

- 2. One mechanism drug companies have to improve certainty about the agency's acceptance of certain clinical 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?**

BIO conducted a survey in late 2013 and found that only 26 % of survey participants have utilized a SPA. Among those that had 78% had to go through multiple submissions and review creating delays in the clinical development program. There is also growing concern that these agreements are not always upheld so it may not be worth the time and effort required to reach an agreement with FDA on a SPA. While there are times where a significant scientific finding would require that a SPA not be upheld we should examine how to improve the SPA process to ensure communication occurs throughout the clinical program under SPA to enable sponsors to adjust if necessary in a manner that minimizes delays and duplicative activities and best enables the program to advance if appropriate.

- 3. What barriers are currently in place that limit that 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?**

As discussed in Question 1, integrating approval requirements with post-market approval requirements would incentivize efforts to collect real-world evidence in a more robust manner. FDA should be working with industry, physicians, patient organizations and other stakeholders to develop methodologies and/or criteria for the utilization of real-world data from sources such as clinical trial registries, electronic health care records and claims databases to conduct virtual clinical trials in the post-approval setting. This could serve to enable approval based on reasonable clinical trial sizes that maintain FDA's gold standard for safety and efficacy and also ensure that information continues to be collected that will allow for analysis and refinement of risk/benefit profiles in the real world.

- 4. In your testimony, you touch on the need for certainty after approval and the challenge of ensuring that there is coverage of a new drug or device by Medicare, Medicaid or private insurance. Typically, commercial insurers cover something that Medicare covers. What are the challenges that are faced getting covered and reimbursed under Medicare?**

One of the biggest challenges with reimbursement for medical devices is the data requirements payors (both government and private) impose before granting coverage because the requirements are often unclear and so high. Also, payors want to see more data and diffusion of a new technology until they agree to provide coverage for it, while physicians and hospitals will not agree to use the product unless they get paid. Equally challenging is that data and utilization requirements are very ambiguous. There is also increasing evidence that payors are raising the standard for coverage determinations.

With regard to molecular diagnostic tests, there exists considerable uncertainty regarding both the standards for coverage by CMS, and also the amount of payment provided for covered tests. Recently, Congress passed the Protecting Access to Medicare Act of 2014, which created a new, market-based system for pricing molecular diagnostic tests. Although this legislation is a substantial step forward towards recognizing the value that these tests provide the healthcare

system, there are many issues in this legislation that must be interpreted and resolved by CMS to ensure adequate appropriate payment amounts are met. I encourage the committee to remain abreast of the developments in implementing this legislation, and responsive to stakeholders that raise issues as they arise over the next couple of years.

Even if this new system creates an adequate and appropriate payment amount that recognizes the value of molecular diagnostics, the standards of evidence by which these tests are covered by CMS remain unclear. Under the relevant statute, CMS must cover products and services that are "reasonable and necessary" to the treatment of Medicare beneficiaries. This results in broad discretion to CMS to set the evidentiary standards for the products and services they choose to cover, which typically occurs via third party contractors. This results in a system with multiple contractors setting independent coverage policies in different regions of the country, and the standards for evidence required for coverage are not uniform. Further complicating the coverage issue for investors and test developers, CMS lacks adequate transparency regarding the standards used and the rationale of why particular coverage decisions are made. In many cases, CMS and its contractors demand levels and amounts of evidence that a diagnostic business model simply cannot consistently provide. Indeed, the markets for diagnostic tests are many times much smaller than those for therapeutic interventions.

The lack of certainty regarding payment and coverage for molecular diagnostic tests disincentives investors from entering this market. If investors do not have a reasonably clear picture regarding what milestones the test developer must hit to see a return on investment, they are likely to look to other markets. It is critical that CMS better define evidentiary standards that recognize the value that molecular diagnostics provide to the healthcare system, create clear and attainable metrics for achieving coverage, and increase transparency into the rationale for individual coverage decisions.

5. You mentioned that in Europe they have something called the adaptive licensing pilot program and that could help modernize our regulatory system. Would you talk more about this program and how it could be used in the United States?

In March, 2014 the European Medicine Agency (EMA) announced its "adaptive licensing pilot project," an initiative intended to grant earlier access to medicines meant to treat unmet needs. EMA's adaptive licensing framework calls for the authorization of medicines for restricted (i.e. niche) patient populations followed by "iterative phases" of approval. The agency stated that, "The approach seeks to maximize the positive impact of new medicines on public health by balancing timely access for patients, with the need to provide adequate evolving information on their benefits and risks." The EMA has also postulated that earlier approvals would support subsequent (i.e. broader) approvals by allowing sponsors to collect real-world use data, EMA postulated.

In June, 2014 the EMA announced that they have selected two drugs to enter into the pilot program. There are at least 11 drug applications still under consideration. The agency stated it will contact the sponsors of the selected applications to explore how adaptive licensing can be developed for these specific medicines, with input from multiple stakeholders including health technology assessment (HTA) bodies and patient organizations.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) has also been engaging

in information gathering activities undertaken to inform the development of their own adaptive licensing pilot program.

This type of pathway has the potential to incentivize investment, especially in drugs that treat chronic/progressive diseases. Congress should consider directing FDA to establish a similar pilot program.

Again, thank you for the opportunity to testify and please let me know if I can provide any additional information.

Sincerely,

Alexis Borisy
Partner
Third Rock Ventures