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gene-therapies.org

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VIA ELECTRONIC DELIVERY

Director Wilson Bryan, MD
Office of Tissues and Advanced Therapies
Food and Drug Administration, Center for Biologics Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Director Bryan:

The Institute for Gene Therapies (IGT or "the Institute") is pleased to submit these comments to the US Food and Drug Administration (FDA) on the FDA CBER OTAT Patient-Focused Drug Development Listening Meeting — Patient Perspectives on Gene Therapy Products ("FDA Listening Meeting") held on November 15, 2022.[1]

IGT was launched in February of 2020 to advocate for a modernized regulatory and reimbursement framework that encourages the development of transformative gene therapies and promotes patient access. Through a Corporate Advisory Council, Patient Advocacy Advisory Council (PAAC), and Scientific, Academic & Medical Council (SAMC), the Institute represents a wide array of patient advocacy groups, gene therapy manufacturers, and scientific, medical, and academic stakeholders seeking to advance the promise of gene therapies. In fact, four members of our PAAC were among the speakers at the FDA Listening Meeting – Annie Kennedy, EveryLife Foundation for Rare Diseases, Jennifer Farmer, Friedreich's Ataxia Research Alliance, Aviva Rosenberg, Gaucher Community Alliance, and Jennifer McNary, parent of sons with Duchenne Muscular Dystrophy. A full list of our members is available at https://www.gene-therapies.org/advisory-councils.

IGT is devoted to promoting the value of transformative therapies and advocating for policies and practices to ensure patient access to these treatments. The most vulnerable patients and their families anxiously wait for the life-altering treatments that gene therapies will offer to some of the most debilitating or rare diseases.

IGT commends FDA CBER OTAT for its efforts to understand patient views on the development and regulatory review of gene therapies. The FDA Listening Meeting was an important opportunity for patients, caregivers, patient advocates, and other stakeholders to share their understanding and expectations regarding gene therapy risks and benefits and involvement in clinical study design and execution for these products.

There is significant and growing interest in gene therapy among patients, particularly the rare disease community, as evidenced by the 46 speakers on the FDA Listening Meeting agenda and many virtual participants.

[1] Food and Drug Administration, "FDA CBER OTAT Patient-Focused Drug Development Listening Meeting — Patient Perspectives on Gene Therapy Products," (Nov. 15, 2022); available at: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-cber-otat-patient-focused-drug-development-listening-meeting-patient-perspectives-gene-therapy.

The speakers, who spanned a number of rare diseases, called FDA's attention to several topics of interest relevant to the four public comment sessions: 1) understanding of gene therapy risks and benefits, 2) involvement in clinical study design and execution, 3) tools to capture patient experience data, and 4) how to leverage tools to capture patient experience data in clinical studies.

The Institute would like to highlight two key themes that were expressed by several patients, family members, and rare disease community representatives.

There are unique benefit/risk considerations for patients living with rare diseases.

Today, most gene therapies in the later stages of clinical development and regulatory review address rare diseases. The reality for the vast majority of rare diseases is that there are no FDA-approved treatments available. Speakers noted that patients' risk tolerance is always specific to their condition, and that the existence of FDA-approved treatments plays a significant role in that risk calculation. Speakers also highlighted the need to consider meaningful benefits that help patients live more independent lives, such as preserving upper body strength and slowing disease progression for as long as possible. Several speakers provided insights on the level of risk tolerance and views on benefit among the rare disease community as a whole or their own disease community:

- "If we do not embrace these regulatory tools, these therapies may never be developed, and millions of rare disease patients will be left without treatment option, as we've heard throughout the day, significant data collection efforts have been undertaken by stakeholders to quantify patient and caregiver tolerance for risk and uncertainty as related to specific diseases, saw populations and experimental therapies. We must ensure that this patient preference data is considered carefully as a part of the regulatory review and the benefit, risk framework… [C]ommunities understand the risk of doing nothing is certain, and that it is worth risking." **Annie Kennedy, EveryLife Foundation**

- "We do understand the risks and benefits of gene therapy. We realize it is not a cure. We understand dosing challenges. We understand the potential toxicity issues, but the biggest risk that we and our children face is the risk of doing nothing. That risk is 100 percent fatal. A slow, excruciatingly painful death. A long goodbye, if you will…We have to keep the needle moving forward. We need a pipeline for a lifeline and gene therapy is part of that pipeline. So you ask us if we, as parents, understand the risks of gene therapy. We do. But can I challenge you to entertain another question? Does the FDA understand the risk and ethics of not doing anything, and by doing nothing, we are ultimately sentencing these children to death. And when we weigh one against the other, the risk of not doing gene therapy far exceeds the risk of administering it." **Suzette James, Parent of CLN2 Batten Disease patient**

- "And when it comes to gene therapy and Duchenne, being the mother of an older and more advanced patient, our tolerance for risk is incredibly high. I know what's happening without intervention because I see it every day in our community. These young men pass away at alarming rates. My expectations are realistic. I believe that having access to gene therapy early before muscle loss produces a much higher benefit, of course, as with any intervention, but I also believe, as long as there is muscle to preserve, there is value in doing so." **Jennifer McNary, mother of two sons with Duchenne Muscular Dystrophy (one son is in a gene therapy clinical trial)**

Patients need a fit-for-purpose approach to clinical development of gene therapies.

Currently, FDA guidance recommends placebo-controlled clinical studies as part of the development of investigational gene therapies. A number of speakers expressed support for more flexibility in clinical trial designs. They noted that placebo-controlled studies are not without risk and may be unethical in the case of gene therapies for rare diseases. Especially for diseases where there is a strong understanding of the natural history, speakers conveyed their support for alternatives to placebo-controlled studies. Speakers also voiced concerns about the amount of time it takes to bring these therapies to patients and advocated for the use of surrogate endpoints to support accelerated approval and the use of platform approaches where possible.

- "While I respect FDA's conservative approach towards risk and efficacy, I'm concerned that the traditional models may not be appropriate when it comes to novel interventions such as gene therapy and the requirements of ultra-rare conditions. Placebo or sham-controlled trials (where the operation to "insert" the "gene therapy" into the child is faked) expose an already fragile child to an invasive procedure to only receive placebo, and completely undermine the risk-benefit equation. Furthermore, enrolling a child in a gene therapy trial "may rob them of their only chance" for treatment, as "they will most likely succumb to the disease before it is unblinded and they can go to active drug." **Johann Mentz, WWOX Foundation**

- "A majority of parents surveyed by the Foundation [for Angelman Syndrome Therapeutics] (69%) were not willing to pursue a gene therapy for their child if it included a "sham control" and 61% were unwilling to enroll their child if the trial included a placebo control." **Allyson Berent, Foundation for Angelman Syndrome Therapeutics**

- The placebo-controlled trial design for ultra-rare diseases is a huge impediment…It really discourages any other drug developers into our space when they see how ultra-rare it is and then when the traditional placebo control design is the requirement. It really is just going to delay for us...
  We encourage patients all the time to do natural history studies. We're always encouraging that, but what good are they if you can't use them in these innovative ways?... In many of the [Limb Girdle Muscular Dystrphy] subtypes, it's hard to rely on functional outcome measures because it would take years to show improvement. If you looked at a measure like walking or ambulation, the variability between patients will mask a treatment effect…There are possible solutions for LGMD with clinical trial designs…use surrogate endpoints and biomarkers, such as protein expression in biopsies, for accelerated approval versus waiting for functional outcome measures to show benefits." **Kathryn Bryant Knudson, Speak Foundation**

- **"**We're losing the pharmaceutical industry because of the costs of getting things through FDA. In the severe combined immunodeficiency (SCID) space, one clinical trial that successfully treated 50 children was "dropped" by a sponsor due to financial barriers. "These are areas where we really need to rethink the process…because the traditional method is not working for gene therapies." **Barb Ballard, SCID Angels for Life**

- "FDA guidance documents – including rare diseases, natural history studies for drug development and human gene therapy for neurodegenerative diseases, and many others – acknowledged the opportunities for using such natural history, data, and clinical development. However, there seems to be a gap in reducing this to practice, especially when considering leveraging such data sets and control or comparator arms for trials. We're in agreement with FDA guidance and recommendations that optimal study design is randomized and control, so that results can be quickly and accurately interpreted, and that innovative and adaptive designs may also be employed to facilitate product development. We would like to work with FDA

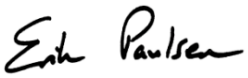
to identify mechanisms where such trials and data sets can be used to inform and supplement adaptive design approaches such as Bayesian methods of borrowing historical data. These novel methods of borrowing data to supplement comparator arms can address some of the challenges in conducting trials and rare diseases, specifically reducing the size of placebo arms and overall number of participants, time and resources to conduct the trials." **Jennifer Farmer, Friedreich's Ataxia Research Alliance**

- "We urge CBER to continue to embrace the regulatory flexibilities and many tools FDA has at hand to overcome these challenges in order to bring these promising therapies to patients as soon as possible. Novel trial designs, including alternatives to placebos, the use of surrogate biomarkers, the expansion of the complex innate design program, and platform approaches." **Annie Kennedy, EveryLife Foundation**

The Institute and our member organizations are grateful to FDA CBER OTAT for its commitment to action-oriented, meaningful engagement with rare disease patients and their families. Patient engagement in the regulatory review process is even more critical in the context of gene therapies, which are advancing rapidly and are already showing the ability to change the lives of patients with rare diseases.

It's critically important that safe and effective gene therapies are approved by the agency as quickly as possible without the impediment of legacy processes that do not apply to today's science. Patients who lack treatment options are waiting. As FDA CBER OTAT continues its thoughtful review of investigational gene therapies, the Institute welcomes the opportunity to engage with you regarding these important areas of interest to the patient community.

Sincerely,



Erik Paulsen
Chairman
Institute for Gene Therapies