American Society of Gene + Cell Therapy

May 2, 2024

The Honorable Brett Guthrie
Chair, Subcommittee on Health
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington DC 20515

Dear Congressman Guthrie,

It was an honor to appear before the Subcommittee on Health on February 29, 2024, on behalf of the American Society of Gene & Cell Therapy. The hearing, "Legislative Proposals to Support Patients with Rare Diseases," provided a critical opportunity to highlight the promise and challenges of transformative cell and gene therapies.

I want to thank you and Representatives Latta, Bilirakis, and Eshoo for sharing additional questions for the record. I am pleased to provide additional information on this exciting field of medicine; please see my full responses below.

Sincerely,

Terence Flotte, MD
Vice President, American Society of Gene & Cell Therapy
Provost & Dean, University of Massachusetts Chan Medical School

American Society of Gene + Cell Therapy

The Honorable Brett Guthrie

(1) Your testimony suggests some need for the FDA to exercise a degree of regulatory flexibility in its process for trials of rare disease treatments or drugs. In a scenario where a treatment or drug was developed, and has shown safety and efficacy for one rare disease in Phase 1-2, but also shows promise for wider application, should there be such flexibility to proceed with the original purpose as a primary endpoint even while adding targets to test for wider application?

(1a) In addition to your testimony, advocacy for such flexibility appeared in two published submissions to the New York Times in the days leading up to the hearing.

- **Links:**
  - **i. Opinion | Gene Therapies Could Transform Rare Diseases. Are We Holding Them Back? - The New York Times (nytimes.com)**
  - **ii. Opinion | Three Mothers' Plea to the F.D.A.: Save Our Children - The New York Times (nytimes.com)**

There are two scenarios where this concept of generalizing a rare disease treatment could apply:

- The first is with a disease-modifying therapy which has the potential to reverse or arrest consequences of a disease process. For example, one might think about a gene therapy or molecularly-targeted therapy for one rare cancer that could be used, as is, for another rare cancer. In this case, the approach may differ depending on the phase of development. For already approved products, the FDA would be "expanding the label" for a specific drug or biologic, meaning they've approved a drug for other indications. This should be given special consideration if the small numbers of patients available for trials to support the expansion make it difficult to prove benefit in conditions beyond the original disease target. For products still under development for the primary indication, there should be flexibility to collect data to support use in other populations, such as in other indications or other age groups while maintaining the initial trial population.

- The second approach is with a platform for a gene therapy product. In rare single-gene diseases, the actual therapeutic gene to be delivered (the "payload") will be different for each distinct disease. In many cases, however, the same carrier system (vector) can be used at the same dose and by the same route of administration for more than one condition. Ideally, under FDA's new authorities granted by Congress in FDORA,[1] platforms like these will be assessed and granted new designations so that different drug products using the same platform can be approved more quickly, thus improving access.

There are two examples of gene therapies approved by FDA to treat multiple diseases: bluebird bio's Zynteglo and Lyfgenia and Vertex's Casgevy. In the first example, Zynteglo was approved in August 2022 to treat transfusion-dependent beta-thalassemia, while Lyfgenia was approved in December 2023 for sickle cell disease (SCD). Both SCD and beta-thalassemia affect the hemoglobin in red blood cells; though their clinical symptoms differ, both can be treated by the addition of a functional beta-globin gene. The two therapies can therefore use the same vector

[1] Consolidated Appropriations Act. 21 U.S.C. § 356k. (2023). https://www.congress.gov/bill/117th-congress/house-bill/2617/text

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and genetic payload to treat completely different diseases; however, because the manufacturing processes differ, they are considered distinct products. The second example, Casgevy, was approved as a single product with two indications, one for SCD and one for beta-thalassemia. The differing approaches of the Agency in assessing vector and payload-based products demonstrate that as the field continues to grow, regulatory pathways will need to be refined over time.

(1b) Following up, can you comment on the breakthroughs in gene therapy for cystinosis and whether the risks and opportunities described in your testimony may apply to this rare disease's treatment, currently making its way to Phase 3?

I do not have first-hand knowledge of the trial you're referencing, though Avrobio did present positive data from their Phase 1/2 trial for Cystinosis[2] at the ASGCT 26th Annual Meeting.[3] Flexible, and responsive regulatory pathways have the potential to make a positive impact on a wide variety of rare diseases.

(2) Dr. Flotte, in your testimony you talk about running clinical trials involving a very small number of pediatric rare disease patients. You highlighted that we need to ensure that we have the right regulatory processes in place for these unique situations. As I understand it, there are actually individualized, or so-called "N of 1" therapies being developed and that the equivalent of the FDA in the UK recently launched a pilot program "to develop a pathway for children with rare conditions to access therapies made specifically for them." Do you have any thoughts the UK's Rare Therapies Launch Pad and whether this type of development and review pathway is something that we should be considering in the US?

- **Link:**
  - **i. Pilot launched to support children with rare conditions to access… (genomicsengland.co.uk)**

Indeed, the N-of-1 trial approach has been approved for some first-in-human gene therapy studies. It is my personal belief that FDA should consider whether an approach similar to the UK's would be appropriate for researchers in the United States.

- I have been in dialog with researchers in the UK and Europe about these approaches, including Dr. Claire Booth at Great Ormond Street Hospital in London, Alessandro Aiuti at San Raffaele Telethon Institute for Gene Therapy in Milan, and others who have formed the AGORA Initiative. Their goal is to enable academic medical centers to continue offering rare disease gene therapies to patients- even in the absence of a corporate sponsor.
- My view is that this pathway should be made clearer to researchers contemplating offering such therapies across the globe. It would be helpful if they were offered more direct guidance from national regulators on how to accomplish this.

[2] ClinicalTrials.gov. (2023). *Stem Cell Gene Therapy for Cystinosis*. https://clinicaltrials.gov/study/NCT03897361
[3] AVROBIO. (2023). *AVROBIO Announces Positive Data from Phase 1/2 Clinical Trial of Investigational Gene Therapy for Cystinosis at the ASGCT 26th Annual Meeting.* https://investors.avrobio.com/news-releases/news-release-details/avrobio-announces-positive-data-phase-12-clinical-trial

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The Honorable Robert Latta

(1) How does a bill like the MINI Act further precision/personalized medicine so that the right patient receives the right treatment, at the right time?

ASGCT does not have a formal position on the MINI Act. The bill is one of a series of measures that would provide an incentive to biotech and pharmaceutical companies to pursue molecular-targeted therapies for rare diseases.

(2) How can we also ensure that the IRA's price setting construct does not impact the ability of other highly innovative drugs, such as cell and gene therapies, to come to market?

ASGCT does not have a formal position on the Inflation Reduction Act. Ideally, legislative proposals impacting therapeutic development should strike a balance, such that there is a sufficient return to drug developers to incentivize investment in R&D for rare disease therapies, but in the long-term a pricing structure that does not disincentivize their ultimate use.

(3) I am glad to see more attention paid to ensure ALS patients are able to get specialized care from Medicare providers. This is an extremely important aspect of any ALS diagnosis – getting timely treatment to extend the quality of life for as long as possible. Can you comment on how well FDA is doing at engaging with new ALS treatments and moving those through the approval process? While the FDA work is ongoing, are they becoming available for trial?

The development of new molecularly-targeted therapies for ALS has been the focus of much research at my own institution and among many ASGCT members. Some ALS-specific gene and oligonucleotide therapies are making it through to the clinical trial process. Measures that can speed up clinical testing and approval of such therapies would be welcome. The narrow time window for each individual patient argues strongly for allowing therapies to proceed with surrogate endpoints and outcomes that even modestly extend quality of life.

(4) What do you see as the potential for greater use of the vouchers over the next five years to incent drug development for pediatric rare cancers such as brain tumors?

The rare pediatric disease (RPD) priority review voucher (PRV) program has great potential to boost development of a wide range of rare pediatric diseases, including both pediatric brain tumors and single-gene disorders. It would be greatly beneficial for the program to be extended.

The PRV program does not require any government funding. When a qualifying pediatric drug approval results in the awarding of a PRV, that PRV may then be sold on the open market, resulting in a monetary benefit for the sponsor. The PRV sale can offset much of the R&D cost that went into developing the product. Those offset costs come after the pediatric rare disease therapy is approved. Our hope is that as more rare disease therapies come to market, more of these PRVs will be awarded, providing a positive feedback loop enabling re-investment into other pediatric rare diseases.

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The Honorable Gus Bilirakis

(1) Your testimony discusses the recent scientific advances in cell and gene therapies, and with your background in pediatrics I'm sure you see the daily quality of life issues these patients and their families face. While we await more game-changing technologies coming to market, I hope we don't also lose sight of the fact that pediatric patients need new treatments to lower their disease burden now. Products that improve their daily life, that lower the amount of steroids and other harsh drug regimens they are currently forced to take on, or ones that have fewer side effects, also deserve the FDA's undivided attention. That's why we should be streamlining the FDA's processes when it comes to rare disease, and we should ensure that FDA incorporates patient-experience data into their benefit-risk assessments. I am proud to cosponsor the BENEFIT Act, which will ensure FDA incorporates this data in its benefit-risk assessments. Would you agree that FDA should take this into account, and can you tell us the importance of incorporating real-world evidence in clinical trial settings?

Many patients with degenerative diseases have a limited window of opportunity to benefit from therapeutic intervention. For that reason, therapies that are shown to provide benefit, even if that benefit is short of curative, should be considered by FDA in the context of rare diseases. Accelerated approval can be a pathway to speed access while additional research is ongoing. Real-world-evidence endpoints, developed with patient input, should be utilized by drug developers and regulators to determine whether a therapy can improve patients' quality of life. I gave an example of this in my written testimony to the Committee:[4]

> "Addressing the challenges and opportunities of interpreting clinical data for rare diseases and CGTs requires flexible approaches and collaborative efforts to enhance safety and efficacy assessments. As one example, I will describe how a gene therapy for a rare genetic cause of blindness received FDA approval. Patients with this genetic disorder first lose the ability to see in dim light. When the first patients in an initial clinical trial were treated, the investigators found the patients could navigate in dim light without running into furniture or other obstacles. This is not a function that is typically evaluated in ophthalmology trials. Working hand in hand with FDA regulators under the leadership of Dr. Celia Witten and Dr. Peter Marks, of the FDA Center for Biologics Evaluation and Research (CBER), the sponsor and physicians involved in the gene therapy program developed a completely new test called the multi-luminance mobility test (MLMT).[5] This test demonstrated the effect that the patients were experiencing in a robust and reliable manner that aligned with the ophthalmology field's experience with functional vision. The MLMT was the critical proof of effectiveness that resulted in FDA approval of that gene therapy – it was the first in vivo gene therapy to ever be approved in the US. In addition to proving the benefit of that one product, this achievement proved the paradigm that patient experience could be assessed in an objective way that met the long-standing FDA standard of a safe and effective therapy."

[4] Flotte, T. (2024). *Written Testimony of Terence Flotte, MD, Vice President of the American Society of Gene and Cell Therapy: United States House of Representatives Committee on Energy and Commerce, Subcommittee on Health, Re: "Legislative Proposals to Support Patients with Rare Diseases."* https://d1dth6e84htgma.cloudfront.net/Terence_Flotte_Witness_Testimony_02_29_2024_54c80c321b.pdf

[5] Chung, D., McCague, S., Yu, Z., Thill, S., DiStefano-Papper, K., et. al. (2017). *Novel Mobility Test to Assess Functional Vision in Patients With Inherited Retinal Dystrophies*. https://pubmed.ncbi.nlm.nih.gov/28697537/

(2) Oftentimes, securing funding for rare disease research can be difficult, particularly for cell and gene therapies, and orphan drug development is often more costly and lengthy than non-orphan therapies. How has the prospect of receiving a rare disease PRV attracted funding for rare disease drug development?

The rare pediatric disease (RPD) priority review voucher (PRV) program has great potential to boost development of a wide range of rare pediatric diseases. A recent research paper demonstrated that a significant portion of PRVs granted so far have been for gene and cell therapies.[6]

The PRV does not require any government funding. When a qualifying pediatric drug approval results in the awarding of a PRV, that PRV may then be sold on the open market, resulting in a monetary benefit for the sponsor. The PRV sale can retroactively offset much of the R&D cost that went into developing the product. Our hope is that as more rare disease therapies come to market, more of these PRVs will be awarded, providing a positive feedback loop enabling re-investment into other pediatric rare diseases.

(3) As you know, 95% of the 10,000 known rare diseases currently do not have any FDA approved treatment. Considering the dire need to have safe and effective therapies for rare disease patients, how important is it to have the correct incentives in place for companies to research rare diseases, especially for children?

This point is very well made. The incentives that have been approved by Congress to date have been very helpful, as would many of the other proposals that have been floated over the years. But given the sheer number of rare diseases needing treatment, there needs to be more bandwidth in rare disease drug development - so more incentives are called for overall.

(4) Why does it take time to see the impact of a policy like the rare pediatric PRV?

Pediatric PRVs are awarded to a sponsor at the time of a successful biologics licensing application (BLA) or new drug application (NDA) – in other words, once FDA approves the therapy. The PRV may then be sold on the open market, which results in a monetary benefit that can offset much of the R&D costs to develop the drug. The system results in a time lag, as a sponsor must take a product all the way through approval before they can even attempt to sell the voucher. Our hope is that as more rare disease therapies come to market, more of these PRVs will be awarded, providing a positive feedback loop enabling re-investment into other pediatric rare diseases.

(5) Will providing an additional four years allow for a more robust evaluation of the rare pediatric PRV program's impact?

Yes, the retroactive nature of the PRV means that a drug developer must decide to invest in a pediatric rare disease therapy 5 to 10 years earlier than they can realize the monetary benefit.

[6] Mease, C., Miller, K. L., Fermaglich, L. J., Best, J. Liu, G. & Torjusen, E. (2024). Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: Designations, diseases, and drug development. *Orphanet Journal of Rare Diseases, 19*(86). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10895788/pdf/13023_2024_Article_3097.pdf

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(6) The FDA's review process is often inconsistent between its many review divisions, which has a negative impact on companies trying to develop new therapies. What can be done to help make FDA's review processes more consistent and predictable while still maintaining their emphasis on safety and efficacy?

Alignment in the review of all molecularly-targeted therapies (gene therapies, cell therapies, oligonucleotide therapies and molecular-targeted small molecule drugs) would be broadly positive, as it would lead to more consistent outcomes for researchers and drug developers who are testing multiple different therapeutic platforms in an attempt to treat a rare disease.

A recent example of the inconsistencies between FDA centers appeared in the Advanced Manufacturing Technologies (AMT) Designation Program draft guidance for industry.[7] In that guidance, there are several instances of imbalances in the AMT pathway between Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER). In comments submitted to the Federal Register,[8] ASGCT expressed our concerns that the draft guidance was unduly limiting for BLA applications compared to drugs on the New Drug Application (NDA) pathway:

> "In the draft guidance, FDA states that a BLA "should not incorporate by reference a designated AMT, including by referencing a DMF that contains a designated AMT" because "a BLA holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license." This is directly contrary to the authorizing statute, which "allow[s] the holder of an advanced technology designation, or a person authorized by the advanced manufacturing technology designation holder, to reference or rely upon, in an application submitted under Section 505 ***or Section 351 of the Public Health Service Act*** [emphasis added], including a supplemental application, data and information about the designated advanced manufacturing technology for use in manufacturing drugs in the same context of use for which the designation was granted."
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> This policy, if finalized, would be restrictive to the CGT field and against the intent of AMT designation to speed progression of standardized and novel manufacturing methods for CGTs to market. We strongly urge FDA to remove this restriction in the final guidance. We also request that FDA revise the 2019 "Drug Master Files: Draft Guidance for Industry" and the rule proposing changes to 21 CFR 601.2 (h) to clarify that cross-referencing Master Files is permitted for holders of, or those with a right-of-reference to, an AMT-designated technology in BLA applications.
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> While the draft guidance is a useful primer for the AMT pathway, it unduly limits the scope and potential of the program and lacks the level of detail necessary for AMT development. Given the novelty and complexity of CGT manufacturing processes, ASGCT would also like to request explicit sections in the final guidance outlining the requirements of the AMT Designation Program for CGT manufacturing technologies.

[7] Food and Drug Administration. (2023). *Advanced Manufacturing Technologies Designation Program: Draft Guidance for Industry.* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-manufacturing-technologies-designation-program

[8] American Society of Gene & Cell Therapy. (2024). *Advanced Manufacturing Technologies Designation Program.* https://www.asgct.org/ASGCT/media/about/AMTDP-Guidance-Comment-Addendum-letterhead-signed.pdf?ext=.pdf

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> The Society would welcome the opportunity to work with the Agency on further developing this pathway to meet its goals for the CGT field."

(7) In January of this year, FDA Commissioner Califf called for "creative approaches" for rare disease therapies, as the current pathways are not optimal. What are some specific ways that the FDA can exercise regulatory flexibility to allow rare diseases therapies to be evaluated quickly?

In addition to Secretary Califf's encouraging statements, ASGCT would like to commend Dr. Peter Marks, Director of CBER, the primary unit that regulates gene and cell therapy. Dr. Marks was recently honored with ASGCT's Sonia Skarlatos Public Service award for his pivotal role in the approvals of gene and cell therapies over the past 7 to 8 years. Dr. Marks has been very proactive and engaged with gene and cell therapy researchers.

That said, there are areas where the regulatory process could be more helpful. This is particularly true of ultra-orphan therapies that are being taken to the clinic by academic health centers when there are no companies interested in investing. Such centers must pursue lower-cost methods to produce and test safe and effective therapies, and they need guidance and partnership with regulators in pursuing those approaches.

Alternative study designs are also an important tool for rare disease therapies. As I noted in my written testimony before the Committee:

> "Keeping in mind the small patient populations, alternative study designs – including decentralized studies, use of RWE (Real World Evidence), and patient experience data – are crucial in advancing CGT research.[9] Clinical trials for CGT products often require specialized infrastructure, manufacturing, and clinical administration facilities, which can further limit patient participation in a traditional trial structure but may be mitigated by innovative trial approaches. Embracing these approaches can benefit patients in need by allowing researchers to accelerate the development and adoption of innovative CGTs and make participation more accessible for a broader, and more representative, population.
>
> Incorporating decentralized study designs can aid researchers in gathering data from patients in their natural environments, which may provide a more accurate assessment of treatment outcomes and long-term safety. RWE can complement the findings from controlled clinical trial settings, enhancing the overall understanding of the therapy's impact. Innovative study designs can also offer a more patient-centered, and efficient way to collect pre- and post-approval safety and efficacy data, ultimately leading to better treatment outcomes.
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> Traditional clinical trials may face challenges in recruiting a diverse range of participants due to geographical limitations or lack of awareness, and these issues are heightened in rare disease trials. Some of the disparities in clinical trial participation, and lack of

[9] American Society of Gene and Cell Therapy (2023). *Comments to FDA on Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on CGT Products Listening Session*. https://asgct.org/advocacy/policy-statement-landing/2023/post-approval-cgt-products-listening-session

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representation in clinical data, stem from logistical barriers (such as lack of transportation, interference with work and family responsibilities, as well as out-of-pocket expenses). RWE, such as RWE derived from registries, has the potential to facilitate the inclusion of more representative patient populations to reflect the risks and benefits of products more accurately.[10,11] These same considerations also are relevant in the post-approval setting, especially for patients living in remote areas who may be less likely to travel to tertiary institutions."

As mentioned previously we would support greater harmonization of regulations for all molecularly-targeted therapies. I highlighted the AMT Designation Program above; ASGCT would be pleased to make some of our member experts available to your office to discuss additional examples.

(8) I was a proud co-lead of the TRANSPLANT Act, which was enacted in 2021 and reauthorized the C.W. Bill Young Cell Transplantation Program and the National Cord Blood Inventory, which provides thousands of Americans access to lifesaving treatments made possible through the use of cord blood. For over thirty years, cord blood cells, collected from the umbilical cord after birth, have been used in transplants to treat over 80 serious diseases, including rare diseases such as sickle cell, thalassemia, Krabbe disease, metachromatic leukodystrophy (MLD), severe combined immunodeficiency (SCID), Gunther disease (CEP), Hunter syndrome (MPS II), Niemann-Pick disease, and an array of immune deficiencies. Continued research into the use of cord blood as a source material for manufacturing various types of rare disease treatments is evolving rapidly, leading to new innovations that have the potential to save lives and offer children impacted by these life-threatening diseases a new hope at life. How have you seen the use of cord blood in treatments improve the lives of children with rare diseases?

Cord blood is a major source for both hematopoietic stem cell transplants (as a substitute for bone marrow) and as a cellular platform for *ex vivo* gene therapy for all the conditions you mentioned. ASGCT appreciates that you and your Congressional colleagues took action to expand access to cord blood through the TRANSPLANT Act. It has been remarkable to see how *ex vivo* gene therapies with genetically modified cord blood have impacted so many conditions. The benefits reach far beyond those conditions like severe combined immune deficiency (SCID) that affect bone marrow-derived cells; they also extend to a wide array of neurologic diseases including those you described here. This is providing life-saving therapy to many children who might otherwise have had no treatment options at all.

[10] American Society of Gene and Cell Therapy (2023). *Comments to FDA on Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Draft Guidance*. https://asgct.org/advocacy/policy-statement-landing/2023/considerations-for-the-design-and-conduct-of-exter

[11] American Society of Gene and Cell Therapy (2022). *Comments to FDA on Real-World Date: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance*. https://asgct.org/ASGCT/media/about/ASGCT-comments-on-FDA-2021-D-1146-Assessing-Registries.pdf

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The Honorable Anna Eshoo

(1) As advanced cell and gene therapies are approved by the FDA to treat adults, additional support is needed to spur similar innovation and investment in gene therapies to treat rare pediatric diseases. That's why I introduced the Creating Hope Reauthorization Act to provide incentives for research and development of new drugs to treat rare pediatric diseases.

(1a) How can we ensure children aren't left out of the new frontier of medicine in cell and gene therapy?

Ensuring children are included in drug development is a vital ethical issue facing our field. Many of us in the research world feel that we have a moral obligation to make the power of gene and cell therapy accessible to any child that needs it. Much of what I have discussed throughout these Questions for the Record relates to how we might improve access for children with rare and ultrarare conditions that are currently being left out.

The other important dimension of access is global access; that is, making it possible for children in countries that are less wealthy than our own to receive the benefits of this technology. A particularly important example of this is the two newly approved gene therapies for sickle cell disease, which is most prevalent in sub-Saharan Africa. During the worst days of the AIDS crisis, the US took the lead through the PEPFAR program to get anti-HIV drugs into lower-resource settings. I hope there may be lessons from the PEPFAR experience that can guide a future approach to global gene therapy for sickle cell disease. That may require "down-scaling" technologies to perform gene therapy, with the goal of developing less expensive manufacturing methods and creating delivery processes adapted to the settings where these therapies are needed.