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IGT
Institute for Gene Therapies

July 23, 2021

The Honorable Diana DeGette
United States House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Fred Upton
United States House of Representatives
2183 Rayburn House Office Building
Washington, DC 20515

RE: Comments on 21st Century Cures 2.0 Discussion Draft

Dear Representatives DeGette and Upton,

The Institute for Gene Therapies (IGT or "the Institute") is grateful for the opportunity to provide comments on the 21st Century Cures 2.0 Discussion Draft and supports Congress' efforts to realize the value of transformative therapies for patients, caregivers, the healthcare system, and society. The 21st Century Cures Act has helped to advance medical research and foster a new era of medical innovations that may ultimately establish new cures for the world's most devastating diseases. Efforts to develop the "Cures 2.0" package continue that legacy, including several policies that would be beneficial to the work of the federal government in response to the current pandemic.

IGT was launched in February of 2020, with a focus on advocating for a modernized regulatory and reimbursement framework that encourages the development of transformative gene therapies and promotes patient access. IGT aims to inform the conversation regarding the value of transformative therapies and advocate for policies and practices that can ensure this value is realized to improve the lives of patients with rare diseases. Our comments focus on Title III: Food and Drug Administration (FDA), Title VI: Centers for Medicare and Medicaid Services (CMS), and Title I: Research, with a specific goal of encouraging patient access to gene therapy and genetic disease screening, as well as establishing modernized reimbursement pathways.

I. TITLE III: FDA

a. Sec. 303. FDA Cell and Gene Therapy

Cell and gene therapies are transforming the way we treat patients suffering from genetic diseases. Numerous therapies are already in clinical development and investment continues to grow in further research and development. It is critical the agency is up to the task and that it is equipped with the budgetary resources and regulatory tools it needs to facilitate timely review of these products so we do not stifle advancement of these therapies. IGT commends Congress taking action to identify resource constraints at FDA. This review would inform Congressional decision-making with regards to authorizing and appropriating funds to the agency, as well as addressing barriers in the current regulatory scheme.

Nonetheless, there are regulatory issues at the agency which Congress could take action on immediately, such as addressing challenges gene therapy manufacturers are currently facing with the current Chemistry, Manufacturing, and Controls (CMC) guidelines, which we address in our comments for Sec. 308 of the proposal, should be made as soon as possible.

b. **Sec. 304. Increasing use of real-world evidence**

Cures 2.0 requires the HHS Secretary to issue guidance on utilizing real-world evidence (RWE) in determining the safety and efficacy of Breakthrough Therapy, Fast Track, and Accelerated Approval drugs. Further, it requires HHS to establish a consistent framework for RWE application in research, regulation, and procurement. Sec. 304 also establishes the Real World Evidence Task Force, a task force to "coordinate the programs and activities of [HHS] with regard to the collection and use of real world evidence." IGT is supportive of this provision, and recommends adding language applying this provision to products receiving a regenerative medicine advanced therapy (RMAT) designations as well. RWE has already shown significant benefit in the post-market setting for providing additional data that support continued access and to satisfy post-marketing requirements. These RWE post-marketing benefits are especially significant for gene therapies due to the challenges of gathering post-market evidence due to the small, heterogeneous patient populations these treatments target.

c. **Sec. 305. Improving FDA-CMS Communication Regarding Transformative New Therapies**

Cures 2.0 requires communication be initiated between the FDA Commissioner and CMS Administrator upon the designation of a Breakthrough Therapy, Fast Track product, or Accelerated Approval product. While IGT supports removing barriers which facilitate immediate patient access to transformative gene therapies upon FDA approval, it cautions that mandating such broad communication or coordination may not have the intended effect of facilitating expedited access and may instead increase the burden on FDA and could delay approval and access of much needed therapies. In federal healthcare programs, such as Medicare and Medicaid, parameters exist to enable coverage at launch for transformative therapies that satisfy statutory criteria; and there is little data the FDA could share with CMS that the sponsor could not provide directly, with the potential for additional burdens on FDA review staff.

Further, the language requires both parties to share information regarding approval and coverage decisions with each other as may be appropriate to inform and coordinate such decisions. While IGT supports communication between FDA and CMS regarding coding decisions, the provision only specifies the expedient exchange of approval and coverage information. IGT recommends that the provision be modified to solely require communication between the agencies in areas regarding expedited code creation by CMS for products granted with either Breakthrough Therapy or regenerative medicine advanced therapy (RMAT) designations or through the Accelerated Approval pathway. This would allow for CMS to expedite work on relevant coding processes that facilitate reimbursement and claims processing when a new treatment is approved, which in turn would streamline uptake of new therapies upon approval. For example, there is approximately a one- to two-year lag between ICD-10-CM diagnosis code introduction and implementation. This timeline is set by statute, resulting in a very structured, but innately slow procedure for updating clinical and procedural codes. As discussed above, Cures 2.0 should accelerate the timeline for establishing new diagnosis codes for disorders treated by innovative, transformative therapies.

d. **Sec. 306. Establishment of Additional Intercenter Institutes at the Food and Drug Administration**

This section would require FDA to establish two new Centers of Excellence (CoE) within the agency, one of which would focus on rare diseases. IGT commends the discussion draft for its recognition that addressing the needs of the rare disease community will require a highly coordinated FDA that incorporates disease-specific knowledge and expertise, including from patients and patient organizations, clinical experts, researchers and manufacturers. IGT believes FDA should place the highest priority on ensuring decision-makers in the review divisions across CDER and CBER have the necessary expertise and understanding to facilitate continued scientific innovation. FDA should be encouraged to increase collaboration and coordination among and within its Centers, and seek opportunities to incorporate expert input into regulatory decision making. We also reiterate that Congress can support FDA in these improvements by providing adequate financial resources, particularly for the Center for Biologics Evaluation and Research (CBER) that is tasked with the review of gene therapies. Taken together, these reforms would advance innovation and spur the development of new therapies, including gene therapies.

e. **Sec. 307. IND Application Not Needed to Initiate Accelerated Approval**

While IGT supports this provision, the current draft only provides technical fixes for products seeking RMAT and Breakthrough designations. IGT strongly believes that products seeking Fast Track designations should be afforded the same regulatory treatment. We recommend adding an additional provision modifying Section 506(b)(2) [Fast Track Designation] of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(b)(2)) in the same manner as Section 506(a)(2) [Breakthrough Designation] and Section 506(g)(3) [RMAT Designation]. Ideally, this addition would achieve the following statute modification.

> ***Fast Track Designation*** **- Section 506(b)(2)**
> The sponsor of a new drug may request the Secretary to designate the drug as a fast track product. A request for the designation may be made **at any point before or after submission of an application for approval of the drug under section 355(b) of this title or licensure under section 351(a)(2) of the Public Health Service Act [42 U.S.C. 262(a)(2)]** ~~concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(3) of the Public Health Service Act.~~

f. **Sec. 308. Guidance Regarding Development and Submission of Chemistry, Manufacturing, and Controls Information for Expedited Approval**

IGT supports the provision to address the critical need for a fit-for-purpose approach to Chemistry, Manufacturing, and Controls (CMC) information for gene therapies. Gene and cell therapies are among the latest medical advancements that have the potential to improve the lives of patients, particularly those suffering from rare diseases. However, manufacturing these therapies presents unique challenges due to the dynamic nature of cell and gene therapy development. Unlike for small molecules, data to inform the optimal manufacturing process accumulates at a different rate and necessitates a more flexible and tailored approach for cell and gene therapies. Therefore, it is critical for the FDA to apply a risk-based, phase-appropriate approach to evaluating CMC data for these products. We strongly support the language allowing opportunities for sponsors to interact directly with FDA regarding the submission

of CMC information throughout the life cycle of the product. Communication between sponsors and the FDA would streamline the submission process and reduce inefficiencies for all parties involved. We recommend the provision could be strengthened by requiring FDA, in addition to its guidance making, to take immediate steps to implement efficient CMC development and review, through phase-appropriate CMC requirements, submission of CMC information, and communication throughout the life cycle of the product.

g. **Sec. 309. Post-Approval Study Requirements for Accelerated Approval**

IGT is supportive of adjusting post-approval study requirements to confirm the predicted clinical benefit of a therapy by permitting the use of real-world evidence, such as patient registries and clinical evidence. Electronic health records, patient registries, pharmacy data, and clinical data generated through mobile medical technology has increased the availability and accessibility of real-world evidence. We encourage Congress to take steps to allow FDA to fully leverage access to RWE in their regulatory decision-making processes.

This section will be particularly beneficial to gene therapy development. For many rare genetic diseases, the pathology is often well understood, making use of surrogate endpoints (i.e. biomarkers) for approval quite applicable, in some cases. This is precisely what accelerated approval was designed for, making gene therapies inherently good candidates for the program.

II. TITLE IV: CMS

a. **Sec. 407. Expanding Access to Genetic Testing**

This section would provide federal support for the use of genetic and genomic testing for pediatric patients with rare diseases using Section 1115 demonstration authorities to establish enhanced pediatric genetic testing programs in up to 5 states. IGT is supportive of this section. Furthermore, we urge Congress to consider opportunities to ensure the entire U.S. newborn screening ecosystem, including the federal Recommended Uniform Screening Panel (RUSP) process and states, can keep pace with transformative new technologies, which could include:

- Public-private partnerships for financing newborn screening pilots and implementation of new conditions;
- Modernization of the RUSP process to eliminate redundancies and accelerate the ability to recommend new conditions, including preliminary RUSP inclusion/or RUSP expansion for conditions with gene therapies in development or that received marketing approval; and,
- Additional funding and support to states to accelerate state compliance with RUSP recommendations.

III. TITLE I: Research

a. Sec. 501. Advanced Research Projects Agency for Health

This placeholder section would establish the Advanced Research Projects Agency for Health (ARPA-H). IGT supports the establishment of an agency whose sole focus is to drive innovative and transformative breakthroughs in medical research and expedite the application and adoption of these breakthroughs. ARPA-H will likely engage in advanced research on a broad number of high-risk, high reward projects, as its' Defense counterpart DARPA (Defense Advanced Research Projects Agency) already does. As Congress continues to formulate the legislation, IGT encourages consideration of language to ensure ARPA-H includes rare genetic diseases with smaller patient populations in its body of research. This is especially important when you consider the challenges facing gene therapy developers. High research, development, and regulatory costs coupled with the assumption of significant risk does little to attract the capital necessary to finance the development of new therapeutics. The high degree of autonomy afforded to ARPA-H could mitigate these market forces by helping advance rare disease research that may not otherwise succeed due to financial or regulatory hurdles.

IV. Additional Comments

a. Federal Healthcare Program Price Reporting Revisions

For a drug or biologic to be payable under Medicaid and Medicare Part B, Section 1927 of the Social Security Act (SSA) requires manufacturers to agree to participate in the Medicaid Drug Rebate Program, the 340B Pharmaceutical Pricing Program, and execute agreements with Department of Veterans Affairs for listing products on the Federal Supply Schedule. Through participation in these programs, manufacturers are required to provide mandatory rebates or offer drugs at established ceiling prices, as well as submit extensive price reporting data to the government as specified by the program. These price reporting methodologies, many of which are based on "per unit" utilization data and computations, were established long before potentially curative, one-time therapies were envisaged in the U.S. While manufacturers of gene therapies coming to the market today must attempt to apply these methodologies to their therapies, these systems are ill-equipped to support a future landscape of one-time therapies, particularly when outcomes-based payment models are considered.

Rather than attempting to fit gene therapies into a system built primarily for chronic therapies and "per unit" methodology calculations, IGT recommends development of a wholly new price reporting approach specific to gene therapies, including those administered under value-based payment arrangements (VBAs). This type of system would provide mechanisms for calculating and providing payment of the financial obligations applicable for a product under relevant mandatory discount, rebate, and ceiling price requirements in federal healthcare programs, without otherwise attempting to apply methodologies that are ill-suited to potentially curative therapies. IGT emphasizes that State Medicaid Programs would still receive the standard Medicaid drug rebate and any inflationary rebate, if applicable, and related obligations to the 340B Program and other federal programs would be fulfilled, but the system would be better tailored to reporting data for one-time therapies, including under potential VBAs.

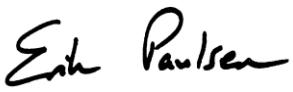
IGT encourages Congress to include provisions in the Cures 2.0 bill that would clarify price reporting requirements facilitating new payment approaches that are appropriate for the oncoming wave of curative therapies. Ideally, these provisions would adjust existing regulatory definitions of price

reporting metrics that pose barriers for VBAs, such as Medicaid Best Price, Average Manufacturer Price (AMP), and unit price, as well as Medicare Part B Average Sales Price (ASP), to define the terms for payments made pursuant to VBAs. Congress should encourage the Department of Health and Human Services (HHS) to provide clarifying guidance on how manufacturers can incorporate VBAs into their price reporting calculations and provide necessary waivers and exclusions (through Sec. 402 and Sec. 1115 waiver authorities) for rebates and price reductions tied to outcomes-based payment metrics. These waivers and exclusions would apply to rebates greater than the standard, mandatory rebate, as highlighted in the preceding paragraph.

Conclusion

IGT appreciates the opportunity to provide input on the 21st Century Cures 2.0 Discussion Draft and looks forward to the opportunity to engage with Congress as this effort moves forward. The Institute supports developing sustainable, flexible, and permanent regulatory and payment pathways that are modernized to reflect the advances in science resulting in such transformative therapies and ensure these innovations reach patients. IGT would be pleased to serve as a resource on gene therapy issues during this process and answer any questions regarding these comments.

Sincerely,



The Honorable Erik Paulsen
Chairman
Institute for Gene Therapies