April 6, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2020-D-2021: Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Draft Guidance for Industry *Human Gene Therapy for Neurodegenerative Diseases* (Draft Guidance or Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO appreciates FDA's efforts to provide drug developers with guidance pertaining to the development of gene therapies for specific diseases, in this case neurodegenerative diseases. While we appreciate that the Guidance covers many critical development issues for gene therapies, much of this guidance is not specific to gene therapies for neurodegenerative diseases, and we are concerned that some stakeholders, including FDA staff, may not be aware of the impact of this Guidance on gene therapy programs outside of neurodegenerative diseases. To this end, as the Agency sets policy in the gene therapy space, we encourage the issuance of (1) broad guidance on gene therapies that includes information that is applicable across diseases and (2) publication of focused and brief disease-specific guidance to provide information to Sponsors on disease-specific issues, as appropriate. This is especially important for clinical aspects, such as study design, dose selection, safety considerations, and study endpoints, that are not as amenable to overarching recommendations. We understand the effort expended and redundancy of work that FDA may be experiencing as individual Sponsors bring the same or similar development questions to FDA via formal meetings. We encourage the FDA to explore ways to quickly identify common issues that are surfacing across programs such that clear and actionable policy can be developed and communicated to the public.

Aspects of this Guidance may also be relevant to cell therapies. We recommend that FDA develop a guidance or Q&A document, that is quickly and easily updated (similar to how the COVID Q&A guidances have been maintained) that consolidates cell and gene therapy policy that has broad applicability into a single document.

We are providing comments on the issues raised in the Guidance, and we realize that many of these comments are relevant to discussions of regulatory policy within FDA that are beyond the scope of neurodegenerative disease. We ask that the FDA ensure that

staff with the Agency that are developing policy on cell or gene therapy development be aware of these comments and the potential applicability to their work.

I. Gene Therapies and Accelerated Approval

FDA notes that "identification and characterization of a surrogate or intermediate endpoint is often challenging" and recommends, in general, use of traditional approval pathways. We encourage the FDA to articulate policy regarding the use of intermediate clinical endpoints for Accelerated Approval for a gene therapy product for which durability of effect is a source of residual uncertainty at the time of approval, and how the policy for gene therapies may differ from regulatory precedent, including regulatory precedent in CDER-regulated products.

There are just a handful of examples of use of an intermediate clinical endpoint as the basis for Accelerated Approval and just a subset of those where durability of the benefit was the primary focus of post-approval confirmatory studies. Analysis of precedent shows that drugs approved on intermediate clinical endpoints evaluated at 4 weeks, 13 months, and 1 year were required to be studied at 54 weeks, 2 years, and 5 years, respectively, to confirm durability of benefit.[1] It is unclear if significant improvement on an intermediate clinical endpoint at 1 year would be sufficient for Accelerated Approval of a gene therapy given the nature of the treatment modality, yet regulatory precedent suggests that this may be sufficient for approval.

We also ask that FDA clarify if products approved via the Accelerated Approval pathway that have not yet converted to regular approval would be considered an acceptable choice of therapy for all participants in an add-on design or if use of placebo is recommended.

II. Preclinical Studies

The FDA indicates that "Additional nonclinical studies may be needed to address such factors as: 1) the potential for developmental and reproductive toxicity…". While it is understood that the Agency has always required Sponsors of gene therapies to carefully assess both the biodistribution and pathology within reproductive tissues to assess risk for germ-line toxicities, separate discrete developmental and reproductive studies have never been a requirement and there is a concern that the language in this Guidance could be adopted for other gene therapies. It would be helpful for the Agency to clarify that the need for any such studies should be guided by the risk associated with the route of administration. For example, systemically administered gene therapies might carry a higher potential risk, whereas locally delivered (e.g., intraparenchymal or intraventricular delivery) may have very low potential risk and therefore developmental and reproductive toxicity studies would not be warranted because the gonads are highly unlikely ever to have exposure to the therapy. It may be helpful for FDA to include reference to early pilot studies evaluating the biodistribution to the reproductive tissues which could help evaluate the need

[1] Remicade, Tysabri, and Exjade, respectively.

for performing developmental and or reproductive toxicity studies balanced with the age of the patient of population and the perceived risk over the lifetime of those patients.
The Draft Guidance also encourages the use of large animal models as they may allow for better assessment of surgical procedures or use of the device for the intended clinical procedure. The use of such animals, while perhaps appropriate, may not provide the statistical power that can be generated from a larger rodent study. Therefore, we encourage the Agency to remain open to the use of either approach taking into consideration the specific product, intended patient population, and what is known about the proposed animal model to be used.

III. Chemistry Manufacturing and Controls (CMC)

While the focus on CMC expectations in the Draft Guidance is appreciated, we recognize that the current advice is too general and does not take into account specific challenges of neurodegenerative diseases, such as the unique route of administration or the higher doses that may be necessary for optimal target engagement. Additional specific examples of risk assessments approaches and/or testing strategies would be beneficial to Sponsors.

We appreciate that the Agency's recommendations regarding CMC are provided with the goal of using early-phase clinical data as evidence of efficacy for approval. We support this approach, and it would be helpful for the Agency to further reinforce when this context is being applied to certain elements of the Guidance. For example, in the course of a typical product development, a full evaluation of critical quality attributes (CQAs) and critical process parameters (CPPs) and implementation of corresponding controls would not be appropriate "during the early clinical development phase." Product understanding evolves during clinical development, and thus fully establishing CQAs is a late-stage expectation. Defining CPPs in early development may be an irrelevant exercise if there are plans to transition to a pivotal/commercial manufacturing process for Phase 3 studies.

The Agency's recommendation to conduct a two-component risk analysis for process changes is concerning, particularly for its implied connection to comparability. Certainly, retaining product samples for future analysis is a sound and reasonable approach to ensure that new learnings and new assays can be applied retrospectively to prior lots. However, this practice differs greatly in intent from a recommendation that a retrospective risk analysis should constitute the second part of a two-part assessment. As currently written, the implication is that comparability might not be demonstrated until a Sponsor completes a not-yet-defined analysis to be done at some future date, which would indefinitely delay introduction of post-change drug product. We would advise separating best practices in retrospective analysis from any discussion of comparability or risk analysis. If it was the Agency's intent to advise Sponsors to set aside materials for retrospective analysis, we suggest that this be stated plainly.

BIO agrees that potency assays are critical to the development and assessment of a gene therapy product. We encourage the FDA to dedicate more time in development to discussions with Sponsors about their potency assay to ensure that the regulatory expectations are clear, practical, and achievable prior to approval.

Additionally, it will be helpful if the Agency revises language in the Guidance concerning plasmids manufactured at a multi-product facility. If the plasmids are manufactured in a multi-product manufacturing facility, a risk assessment for the presence of other contaminating plasmids that may have been co-purified, should be undertaken. Also, should it be deemed necessary, the drug substance manufacturer should ensure that there is appropriate cross-contamination control at the plasmid production and/or release level.

IV. Clinical Studies

While additional clinical guidance is welcome, additional examples and recommendations would be helpful in the areas of innovative trial design, use of historical controls, and pediatric development.

The Agency has noted a number of factors, connected by an "and" clause, that must be considered when using an external or historical control. BIO is concerned that the quality of available historical data is not a key determinant of the ability to use such data as an external control. While we agree that the factors listed in the Guidance are part of the decision-making context for acceptance of historical data as an external control, we believe that the availability of historical data, in cases where the data meet regulatory expectations, should be sufficient justification for use as an external control regardless of the other factors.

In general, a prospect of direct benefit currently requires pharmacology studies to be conducted in a relevant model before enrolling children into a clinical trial. The issue in rare pediatric diseases is that there are often no models available, or these models are exclusive to certain research institutions and not often available to Sponsors. This may delay initiation of clinical trials in children who desperately need intervention. It would be helpful for FDA to address in broad gene therapy guidance, requirements for demonstrating direct benefit as well as alternative methods that can be used for this demonstration. For this specific Guidance, it would be helpful if FDA provided more detail regarding what is meant by prospect of direct benefit in the context of neurodegenerative diseases and approaches that may be taken in the absence of available models. The Guidance could benefit more if FDA could provide some examples to illustrate each concept regarding ethical considerations for conducting investigations in pediatric subjects.

It would also be helpful for FDA to provide acknowledgement that repeat administration of some gene therapy products may not be possible due to the immune response as well as more detail and discussion around these instances to help guide Sponsors in their study design.

The Agency should make clear that patient experience data (PED) is important to inform benefit risk assessment. The Guidance should explicitly state that the Agency is open to considering data that helps bring light to patient perspectives on benefit risk through qualitative or quantitative data to highlight patient perspective on the benefit risk assessment and the relative importance of treatment characteristics during drug development.

The Guidance recommends that Sponsors seek advice from OTAT through INTERACT meetings, however, Sponsor experience has demonstrated that INTERACT meetings are not granted within the scope of FDA's SOPP. Efforts should be made to ensure the examples noted (e.g., discuss issues such as product's early preclinical program) are used a criterion for granting INTERACT meetings. INTERACT meetings appear to be granted for early proof of concept discussion only. The Agency should provide additional examples for when it is appropriate to submit an INTERACT meeting request.

BIO appreciates this opportunity to comment on FDA's Draft Guidance on *Human Gene Therapy for Neurodegenerative Diseases*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
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