Alliance for Regenerative Medicine

April 5, 2021

Docket Number: FDA-2020-D-2101
Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments for FDA Docket Number: FDA-2020-D-2101 for "Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry." 86 FR 549.

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) commends the FDA for the issuance of the Human Gene Therapy for Neurodegenerative Diseases, Draft Guidance for Industry. ARM appreciates FDA's attention to this important developing field.

ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory and reimbursement initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. Early products to market have demonstrated profound, durable, and potentially curative benefits that are already helping thousands of patients worldwide, many of whom have no other viable treatment options. ARM has become the voice of the sector, representing the interests of 380+ members worldwide, including small and large companies, academic research institutions, major medical centers, and patient groups.

Please find enclosed additional recommendations to consider as FDA finalizes the current draft document. Thank you for your leadership and continued commitment to issuing guidance for sponsors navigating the development of gene therapy (GT) products.

General Comments

ARM supports the advancement of guidance and policies that promote clear, timely communication and ensure predictable and efficient regulatory paths to market for gene therapy products as scientific understanding evolves. While this guidance serves as a useful overview of high-level recommendations, specific recommendations with clear examples would better guide sponsors as they navigate GT development. The Human Gene Therapy for

1015 18th Street, NW
Suite 1102
Washington, DC 20036

info@alliancerm.org
@alliancerm

www.alliancerm.org

Retinal Disorders Guidance for Industry[1] is a good example as it focuses on aspects unique to these types of disorders. For contrast, the Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry does not adequately identify considerations and recommendations that may be specific to a rare, rapidly progressing versus a chronic, slowly progressing neurological disease, although the considerations and rationale will likely be very different between these two disease settings.

In addition, we find many of the recommendations in the guidance could potentially be applicable to other therapeutic areas and other advanced therapy modalities. We also encourage the FDA to issue guidance on new recommendations as they are available and not delay the sharing of important information in an attempt to provide a longer or more comprehensive single guidance document. ARM provides comments on the range of issues presented in the draft guidance, but we do not wish to give the impression that this neurodegenerative disease guidance is the most appropriate place to address those comments. Rather, we recommend that our feedback is shared across teams at the Agency that are working on gene therapy guidance such that regulatory policy is developed, articulated, and communicated in topic-specific guidance, as applicable. We remain concerned about the inclusion of policy relevant to other therapeutic areas in a guidance specific to neurodegenerative diseases.

For example, we support the Agency's use of Q&A documents as an efficient means to inform sponsors of current FDA thinking for gene therapy development. As the FDA gains experience with gene therapies, ARM strongly encourages the Agency to identify streamlined and timely mechanisms to surface challenges that are emerging in multiple development programs, develop policy on those issues within the Agency, and communicate them with opportunity for public comment. This practice should also alleviate some of the meeting burden currently facing CBER.

Interactions Throughout Development & Review

FDA encourages pre-submission communication between sponsors and FDA. ARM agrees that "continuous engagement with the Agency can decrease the potential for development or approval delays" and that improved access to early regulatory input is important to achieving alignment prior to clinical study start. There have been challenges for sponsors in securing necessary meetings (e.g., INTERACT meetings, follow up to pre-IND meetings) and engaging with FDA in timely and effective interactions (e.g., teleconference vs. written response only (WRO)), which is especially detrimental to development of complex, novel products like gene therapies. We understand CBER's resource constraints given the high volume of gene therapy INDs. As such, we ask that FDA provide guidance on the issue of engagement that is actionable in the current

[1] Food and Drug Administration. "Human Gene Therapy for Retinal Disorders; Guidance for Industry". https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-retinal-disorders

environment and in advance of PDUFA VII. We strongly encourage OTAT to consider the appropriate level of guidance and interaction required by sponsors when responding to complex issues raised early in development (e.g., potency). In certain cases, WRO may be inadequate for the level of engagement needed to address these questions. In the absence of an opportunity for dialogue or, at minimum, an opportunity for timely resolution of clarifying questions, these early development issues become more complex, which may ultimately delay access to these therapies in patients with unmet medical need.

FDA cites an openness to accelerated approval of a gene therapy "when a suitable surrogate endpoint" is identified for a disease caused by a "well-understood and well-documented monogenic change". Proposals to develop a surrogate endpoint for accelerated approval should be communicated "early in product development, preferably well before initiating clinical trials." Sponsors also increasingly face challenges in securing early interactions which are critical in obtaining feedback necessary to pursue development of surrogate endpoints. FDA should incorporate additional guidance on when in development a gene therapy sponsor should engage the Agency to discuss potential accelerated approval (e.g., preclinical data availability). We also request the Agency provide detailed guidance on the evidentiary criteria for regulatory acceptance of a novel surrogate endpoint (or intermediate clinical endpoint) in the context of a potentially one-time treatment modality (as opposed to the criteria outlined in the Expedited Programs guidance[2]), including in the setting of a rare disease where a first-in-human study may potentially serve as the basis for approval.

ARM encourages FDA to consider publishing more detailed guidance on the scientific elements of Expedited Programs that are uniquely applicable to gene therapy products, similar to EMA's draft toolbox for PRIME marketing authorization applications.[3] Moreover, in noting the "more-frequent interactions with FDA" and the inherently shortened accelerated development timelines for expedited products, it would be beneficial for FDA to highlight areas critical for early alignment (e.g., manufacturing, companion diagnostics, etc.) to avoid unintended delays.

CMC Expectations for Gene Therapy Products

While the focus on CMC expectations in the draft guidance is appreciated, we see opportunities for the guidance to building on existing CMC guidance by addressing specific challenges of neurodegenerative diseases, such as the unique route of administration or the higher doses

[2] Food and Drug Administration. "Guidance for Industry; Expedited Programs for Serious Conditions – Drugs and Biologics." https://www.fda.gov/media/86377/download.

[3] European Medicines Agency. "Draft toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME marketing authorization applications." https://www.ema.europa.eu/en/documents/scientific-guideline/draft-toolbox-guidance-scientific-elements-regulatory-tools-support-quality-data-packages-prime_en.pdf

that may be necessary for optimal target engagement. Additional specific examples of risk assessments approaches and/or testing strategies would be beneficial to sponsors.

On the topic of drug product purity, the guidance recommends that "the GT vectors used to treat neurodegenerative diseases not to be grown in tumorigenic cell lines and the residual host cell-DNA levels be set to less than 10 ng/dose, if possible". This statement is inconsistent with the 2020 FDA CMC for GT Guidance[4] and the rationale for a different policy for neurodegenerative disease gene therapies, i.e., not allowing the use of tumorigenic cell lines, is unclear. We request that FDA aligns policy across gene therapy guidances. We also encourage FDA to avoid duplication of policy in multiple guidances because it will be challenging to update. Instead, we recommend that FDA reference existing guidance and then clearly explain the scientific rationale for any nuances in policy for the therapeutic area. Further clarity is also needed to confirm that the Agency does not intend to preclude the use of tumorigenic cell lines as production systems for neurodegenerative disease gene therapies.

In relation to limiting residual host cell DNA, we recommend that FDA remove the specific limit of 10 ng/dose, as it may be unattainable for gene therapies delivered with a viral vector such as AAV. This challenge is due to the fact that inevitably during production of AAV vectors, using either the mammalian/plasmid transfection or baculovirus/Sf9 production platforms, some level of host cell DNA can become encapsulated and will not be able to be removed during purification process. Therefore, in particular for neurodegenerative diseases where doses are relatively higher than other disease spaces, a limit of 10 ng/dose may be a substantial underestimation of the safe amount of host cell DNA in a rAAV and may prevent beneficial therapies from reaching patients that need them.

Instead, we recommend the guidance state that total residual DNA levels should be controlled and kept at a minimum, unless otherwise justified, and incorporate examples of risk assessment elements and points to consider for justification of residual host cell DNA limits for gene therapy programs. For example, additional testing to sequence any fragment above a nominal size or any known oncogene in the cell line utilized. This aligns with the WHO guideline on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (2013)[5] as well as the 1997 EMA CPMP Position Statement on DNA and Host Cell Proteins (HCP)

[4] Food and Drug Administration. "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications; Guidance for Industry." https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemistry-manufacturing-and-control-cmc-information-human-gene-therapy-investigational-new-drug

[5] "In setting these limits, there should be consideration of the characteristics of the cell substrate, the intended use and route of administration of the rDNA-derived biotherapeutics and, most importantly, the effect of the manufacturing process on the size, quantity and biological activity of the residual host-cell DNA fragments".

Impurities, Routine Testing versus Validation Studies[6]. Ultimately, alignment of expectations among regulatory agencies will be extremely beneficial to deliver safe and effective products to a large number of patients.

The guidance provides examples of residual product-related impurities that should be carefully evaluated. The examples include incomplete viral particles and cellular subtypes. It is unclear what is meant by "incomplete viral particles," but we assume that it may mean "partially packaged vectors." At a recent NCATS workshop co-hosted by FDA[7], the issue of partially packaged vectors was discussed. The FDA representative[8] agreed with academic and industry panelists that partially packaged AAV should not be considered an impurity, but these partial vectors do need to be characterized. The FDA representative agreed that partially packaged vectors are not always a problem with very large transgenes as this may result in partial packaging of functional or self-correcting vector with no change in transduction efficiency. We ask that FDA clarify the discussion of product-related impurities in the guidance, including clarifying what is deemed an impurity. In addition, it would be helpful to have more specific guidance from FDA regarding expectations for characterization of replication-competent AAV (rcAAV) levels.

Additionally, ARM continues to emphasize the need for a risked-based approach to the effect of manufacturing process changes on CQAs for product comparability for GT products. We request additional transparency on FDA expectations for establishing comparability after manufacturing process changes and the types of changes that trigger comparability studies. Additional guidance is requested regarding the different expectations for establishing comparability at different phase of clinical development, and the proper mechanism and timing of comparability protocol discussions during clinical development. While manufacturing of small batches to increase the number of lots produced could improve the statistical power of such comparability analysis, often side by side studies, while considered, may not be achievable due to the limited number of samples available. The sponsors will greatly benefit from examples of alternative approaches that might mitigate the limited size and number of batches available for testing.

ARM agrees that potency assays are critical to the development and assessment of a gene therapy product. We appreciate FDA's desire to have the potency assay fully validated prior to submitting a BLA, but we remind FDA of the practical challenge of getting enough samples to fully validate the potency assay prior to submission of a BLA. 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. Limited opportunities to discuss the specifics of potency assay development have the potential to result

[6] "As far as DNA from continuous mammalian cell lines (CCLs) is concerned, this impurity was considered, in the past, as a risk factor of concerns that residual host DNA may be tumorigenic. Further information, however, now suggests that CCL DNA poses much less of a risk than previously thought and accordingly should be considered as a general impurity (WHO Expert Committee on Biological Standardisation […])."

[7] https://events-support.com/events/NCATS_Gene_Therapies_November_2020

[8] Zenobia Taraporewala, Ph.D. — Acting Team Lead, Chemistry, Manufacturing and Controls (CMC), Division of Cellular and Gene Therapies (DCGT), CBER, FDA

in significant delays to a gene therapy development program. Moreover, it would be helpful to have additional guidance from FDA regarding specific examples of potency assays that could be considered sufficient to support the initiation of early clinical trials (e.g., infectivity, transgene expression) versus those that should be considered necessary for supporting a BLA submission (e.g., quantitative measure of functional activity).

Considerations for Preclinical Studies

While ARM appreciates that CBER has addressed situations where animal models are difficult to develop or inadequate for the disease studied, we request the Agency consider addressing the relevance of new approach methodology (NAMs) such as *in vitro* and *in silica* approaches including the use of technologies such as "organ-on-chip" for gene therapies. Specifically, we ask the Agency for guidance on using non-animal preclinical modeling to ultimately enable first-in-human studies.

We would like the Agency to address when it is appropriate, and when it is not, to use NAMs instead of animal models in the context of gene therapy development. In situations where NAMs are not appropriate, we would ask the Agency to provide general considerations for species selection and establishing the relevance of preclinical species.

Considerations for Clinical Trial Design

While additional clinical guidance is welcome, additional examples would be beneficial for sponsors navigating gene therapy product development, especially in the areas of innovative trial design, use of historical controls, and pediatric development.

On the topic of historical controls, FDA states that, "Trials using external, historical controls for comparison (rather than a concurrent comparator group to which a suitable fraction of enrolled subjects is randomized) may be appropriate under certain circumstances, such as with a GT product intended to treat a rare and serious neurodegenerative disease…". We recommend that this guidance build on the existing FDA guidance in the Human Gene Therapy for Rare Diseases, which outlines when natural historical controls may be used by providing additional examples or considerations of how sponsors may use external controls for neurodegenerative diseases. Further, the guidance allows for use of historical controls in rare and serious neurodegenerative disease when a number of other conditions are met (e.g., unmet need, concurrent control is not practical or ethical), but does not address the ability to use historical controls based simply on the availability of high-quality, relevant data. In cases where high-quality, relevant, fit-for-purpose historical data exist, we believe FDA should permit the use of those historical control data regardless of the size of the patient population, seriousness of the condition, unmet need, and other factors mentioned in the guidance. For invasive routes of administration (e.g., intra-cisterna magna (ICM)), we request further guidance on what criteria sponsors should consider in the decision to use a historical control group instead of a sham procedure.

FDA also asserts that "While comparison to a placebo may be optimal to determine the effectiveness of some products, various strategies may be applied to minimize unnecessary exposure of subjects to placebo". The Agency references the potential use of add-on and crossover trial designs. ARM supports the minimization of placebo exposure through use of novel trial designs as applicable, especially for invasive routes of delivery where a sham procedure may be necessary for blinding introducing additional risk to trial participants. We suggest that FDA clarify what is meant by a crossover trial in the context of a one-time gene therapy product (e.g., is the intention similar to a delayed start or delayed treatment design?) and what expectations there are for sponsors to demonstrate that "disease progression can be clearly identified". Crossover designs are mainly relevant to diseases where there is fast progression versus slower, chronic neurodegenerative disease, which limits the applicability of this design. We would like to reinforce the urgency and public health impacts associated with slowly progressive neurodegenerative diseases and importance of flexibilities for these programs as well. ARM requests that FDA provide thinking on other innovative designs, such as rescue therapy using standard of care, that may be acceptable to minimize duration of placebo while allowing sponsors to demonstrate statistically meaningful improvement over a placebo control. If a gene therapy is used as an add-on to an existing therapy, ARM requests that FDA provide guidance on expectations for demonstrating a meaningful treatment effect. Lastly, in the rare disease setting when add-on designs are not possible due to lack of effective therapeutic options, ARM encourages FDA to exercise flexibility in the use of natural history controls for neurodegenerative diseases.

The guidance states that "When no prior human safety or efficacy data are available, sponsors planning to conduct pediatric trials should provide a rationale as to why adult studies are either not ethical or not feasible." It goes on to say that "it is important that clinical investigations in pediatric subjects address ethical considerations for conducting investigations in vulnerable populations." ARM encourages FDA to incorporate considerations, including disease severity and time course of serious disease manifestations, for when a pediatric first in human (FIH) study may be ethically appropriate and considerations, if any, for the order of pediatric age groups. Neurological diseases may require early intervention in disease course to avoid irreversible morbidity and to demonstrate a meaningful impact on disease progression. Additionally, guidance on pre-symptomatic patient inclusion criteria (e.g., combination of biomarker and genetic data) is requested to aid sponsors in designing studies that intervene early in disease to avoid neurodegeneration, preserve function, and provide data to support a curative treatment indication.

ARM supports the FDA position that first-in-human (FIH) trials for rare neurological diseases can provide sufficient evidence of effectiveness to support a marketing application with appropriate study design, conduct, and results. The guidance states, "a first-in-human trial of a GT product for a rare neurodegenerative disease may provide sufficient evidence of effectiveness to support a marketing application". An example, particularly with adaptive trial design and when a natural history comparator would be appropriate, would be helpful including timing for alignment with FDA on pivotal study design (e.g., pre-IND meeting). For example, for a rare neurodegenerative disease where a FIH study has primary objectives of safety at several dose levels, a sponsor might

be able to adapt the study protocol by removing arms that evaluated doses later determined to be non-efficacious, increasing the sample size for efficacious doses, and adjusting the patient population (either narrowing or broadening). This would enable data from all participants with the selected dose to contribute to the data supporting the BLA.

We are appreciative that FDA provided a robust definition for patient experience data including caregivers, disease research foundation, and patient advocacy organizations. However, we strongly encourage FDA to consider expanding this section to incorporate considerations for use of digitally derived data in the setting of neurological diseases. FDA should also include language on how FDA will potentially use patient experience data in regulatory decision-making. We also suggest that the FDA reference the Patient-Focused Drug Development guidance[9] on collecting comprehensive and representative input and comment further on PED ability to help sponsors understand patient tolerance for risk associated with the GT, preference for administration, patient-reported side effects, and tolerability. Last, additional guidance on how data collected in the post-market setting (e.g., registries) may inform post market requirement or labeling would be valuable for properly planning lifecycle management.

Considerations for Delivery Devices and Development of Diagnostic Testing

ARM thanks FDA for guidance on delivery devices and diagnostic testing that is critically important for administration and subject selections for neurological disease studies. To strengthen the impact of this guidance we suggest the following updates.

- For device/drug product compatibility, it would be beneficial if FDA could provide guidance on the attributes of most interest to incorporate in device testing.
- Given the limitations in batch size for gene therapy products, additional clarity is requested as to whether testing outlier scenarios (e.g., low product concentration, long hold times) would be sufficient to demonstrate compatibility.
- For changing a delivery device during clinical development (i.e., after Ph1) or in product lifecycle management, sponsors would benefit from further guidance on clinical bridging (i.e., need to generate comparative clinical data with the new device or acceptability of in vitro or nonclinical in vivo approaches), accounting for limited ability to conduct clinical bridging trials with gene therapies that are for one-time administration and/or a limited patient population (for rare/orphan diseases and/or specific genetic subsets of patients).

FDA CBER should also consider how existing guidance on combined use with delivery devices (e.g., devices not specified in investigational or commercial labeling) vs. cross-labeling (e.g., specific devices included in labeling for administration) is applicable. As CDRH guidance alone may not be sufficient, ARM encourages CBER to consider sharing additional considerations for

[9] Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry. https://www.fda.gov/media/139088/download .

gene therapy sponsors to consider as they are developing products with cross-labeled devices and/or combined use with existing devices. Such considerations should account for use of existing legally marketed devices within their current intended use (either with investigational or approved gene therapies), expanding the indication of a legally marketed device to include gene therapies (specifically, or generally), and developing a new device either concurrently with an investigational gene therapy or following approval of a gene therapy.

Overall, ARM commends the FDA for developing a guidance to facilitate the development of gene therapy products for neurodegenerative diseases. We have included specific in-line comments in the attached appendix, titled "Appendix 1 – Detailed comments on FDA Guidance". Our members look forward to utilizing your revised guidance in generation of novel therapeutic products. Please reach out to us if you have any questions about our comments or if we can assist the Agency in any way as they finalize this important guidance.

Sincerely,

Robert J. Falb
Director, U.S. Regulatory Affairs

Alliance for Regenerative Medicine

Appendix 1 – Detailed comments on FDA Guidance

Section	Current Text	Proposed Change / Comment	Rationale for Change or Comment
Pg. 2 Para. 2	Thus, the product's CQAs and manufacturing critical process parameters (CPPs) should be fully evaluated and appropriate controls implemented during the early clinical development phase.	Thus, the product's CQAs and manufacturing critical process parameters (CPPs) should be ~~**fully**~~ evaluated and appropriate controls implemented **as** early **during** clinical development **as feasible**. **Appropriate controls and associated preliminary acceptance criteria should be implemented based on the potential CQAs defined further to this evaluation. The list of potential CQAs may be revised as your knowledge of the product increases during development.**	While a list of potential CQAs and CPPs should be established in early phases of development, limits may be broader during early stages and, as product understanding and clinical experience is achieved, product CQA are typically finalized at the BLA stage. Early in development there is insufficient manufacturing experience to establish appropriate CQA/CPPs. Establishment of CQA may be evaluated based on evidence of safety and efficacy, however – this is typically a "living document" through manufacturing process development and manufacturing validation as more experience is gained.
Pg. 2 Para. 2	In addition, innovative manufacturing strategies such as the production of multiple small lots versus a single large product lot may be considered	In addition, innovative manufacturing strategies, **including but not limited to** ~~**such as**~~ the production of multiple small lots versus a single large product lot, **or the**	Manufacture of multiple small lots may not be possible due to raw material availability, manufacture schedule or cost limitations, or result in insufficient material for

	to increase product manufacturing process experience and knowledge.	**use of small scale model for individual unit operations** may be considered to increase product manufacturing process experience and knowledge.	future comparability requirements. Clarify when this can be on specific unit operations and not end to end processing.
Pg. 2 Para. 2	Sponsors should also pay attention to GT products that may have quality attributes with higher variability than small molecule drugs or well-characterized biological products. Given this inherent variability, additional product characterization studies should be considered to establish acceptance limits for the CQAs.	1. "Given **~~this inherent~~ the potential for** variability **in some cases**, additional product characterization studies should be considered to establish acceptance limits for the CQAs." 2. Additional questions: Does FDA mean additional product characterizations studies would be needed for critical attributes or everything that's in the specification?	1. Remove implication that all GT products have all quality attributes with higher variability
Pg. 2 Para. 2	Products used to treat neurodegenerative diseases may have to be administered in small volumes to therapeutic sites, such as the brain or spinal cord. These sites also have reduced clearance of the administered product, and final product volume and formulation are important considerations.	These sites also have reduced clearance and **buffer capacity** of the administered product, and final product volume and formulation are important considerations.	The CSF volume and mixing rate is relatively much lower than blood in circulation, therefore the buffering capacity is much lower.
Pg. 2 Para. 4	GT products may induce inflammatory immune responses against host cells, become latent in neuronal tissues, or cause unwanted gene expression. Some latent GT products also can be reactivated in	GT products may induce inflammatory immune responses against host cells, become latent in neuronal tissues, or cause unwanted gene expression. Some latent GT products also can be reactivated in response to external signals, leading to viral replication,	Neurodegenerative diseases constitute a heterogeneous group of disorders characterized by progressive degeneration of the structure and function of the CNS or peripheral nervous system. This

	response to external signals, leading to viral replication, damage to the host cells, and environmental shedding. We recommend that all GT products for neurodegenerative diseases be designed to reduce inflammatory immune responses, reduce the possibility of becoming latent, and not contain foreign genes (e.g., reporter genes) that do not directly contribute to the biological function of the investigational product.	damage to the host cells, and environmental shedding. We recommend that ~~**all**~~ GT products for neurodegenerative diseases**, where applicable,** be designed to reduce inflammatory immune responses, reduce the possibility of becoming latent, and not contain foreign genes (e.g., reporter genes) that do not directly contribute to the biological function of the investigational product.	language may not be applicable for all neurodegenerative disorders and it may be helpful to provide guidance based on compartments of GT administration (optic or cranial nerve administration).
Pg. 3 Para. 2	Drug product purity should be carefully evaluated early in product development. Purity assessment generally includes the evaluation of residual product-related impurities (e.g., incomplete viral particles, cellular subtypes) and process-related impurities (e.g., residual host cell proteins, host cell DNA, endotoxin).	Drug product purity should be carefully evaluated early in product development. Purity assessment generally includes the evaluation of residual product-related impurities (e.g., ~~**incomplete viral particles,**~~ cellular subtypes) and process-related impurities (e.g., residual host cell proteins, host cell DNA, endotoxin).	Incomplete viral particles, such as partial packaged vectors, should not be considered an impurity, as FDA discussed at a recent NCATS workshop co-hosted by FDA. Methods for assessing incomplete viral particles are not robust in early development, and the impact of the presence of incomplete viral particles on efficiency of transduction is unknow, this could unnecessarily restrict development.
Pg. 3 Para. 3	Product-related impurities in GT viral vector-based products used to treat neurodegenerative conditions include empty and wild type viral particles, and replication-competent viruses. We recommend that specific and	Proposed text change: **"**Product-related impurities in GT viral vector-based products used to treat neurodegenerative conditions **may** include empty and wild type viral particles, and replication-competent viruses.	Mutations found in vectors will have varying significance (e.g., theoretical risk of appearance of hyperactive variants v/s null, mutations in regulatory elements v/s coding sequence. Functional consequences

	accurate assays for the characterization of empty particles (where applicable), product-related variants (e.g., mutations in the viral vectors), and non-recombinant viral particles (e.g., replication-competent viruses, wild type viruses) be established early in the product development cycle.	We recommend that ~~**specific and accurate**~~ assays for the characterization of empty particles (where applicable), product-related variants ~~**(e.g., mutations in the viral vectors)**~~, and non-recombinant viral particles (e.g., replication-competent viruses, wild type viruses) be established early in the product development cycle. **FDA acknowledges that assay limits may be broader during early development when sponsors are still characterizing a product"**	of these are further unknown, and functional assays such as potency will ultimately identify which product lots will be used. It is recommended to outline that assay limits may be broader during early development.
Pg. 3 Para. 2 & 5	Drug product purity should be carefully evaluated early in product development. Drug product identity should be evaluated very early in product development.	Request clarification on when in early product development product purity and product identity should be evaluated. Currently, purity is noted as "early" and identity is "very early" but criteria or considerations, like how product potency is critical "after changes to the manufacturing process", would be informative.	Additional specifics on appropriate development stages for product characterization will improve sponsor-FDA communications and avoid unnecessary delays in development.
Pg. 3 Para. 4	Process-related impurities, such as host cell proteins, may contribute to unwanted immunogenic reactions in the study subject. For this reason, we recommend that the residual host cell protein levels be as low as can be reasonably achieved based on manufacturing experience and results of engineering manufacturing runs.	"For this reason, we recommend that the residual host cell protein levels be as low as can be reasonably achieved based on **process development and** manufacturing experience. ~~**and results of engineering manufacturing runs**~~.	Change "engineering runs" to "process development" since small scale studies may also be leveraged.
Pg. 3 Para. 4	Depending on the location of product administration and the expected low	"Depending on the location of product administration and the expected low	While it has been possible to reduce rcDNA levels in rDNA-derived

	turnover in the neuronal tissue, administered host cell-DNA impurity may be expected to persist for a prolonged period of time, and may contribute to the development of adverse events. As such, we recommend that the GT vectors used to treat neurodegenerative diseases not be grown in tumorigenic cell lines and the residual host cell-DNA levels be set to less than 10 ng/dose, if possible.	turnover in the neuronal tissue, administered host cell-DNA impurity may be expected to persist for a prolonged period of time, and may contribute to the development of adverse events. As such, we recommend that the GT vectors used to treat neurodegenerative diseases ~~**not be grown in tumorigenic cell lines**~~ **using tumor-derived (e.g., Hela) or tumorigenic phenotypes (e.g., HEK293, HEK293T) follow guidance outlined in CMC information for Human GT INDs; Guidance for Industry**[1] and the residual host cell-DNA levels **should** be ~~**set to less than 10 ng/dose**~~ **minimized based on risk assessment**, if possible." [1] https://www.fda.gov/media/113760/download It would be helpful for the Agency to provide examples and/or considerations for risk assessment if the limits are larger than 10 ng/dose, and clearly specify what is intended for continuous, non-tumorigenic cell lines.	biotherapeutics to 10ng/dose, the limit is unlikely to be attainable for a viral-delivered gene therapy product, due to the intrinsic properties of the viral-delivery system. It may be a substantial underestimation of the safe dose of host cell DNA when delivered by rAAV/baculovirus and may prevent beneficial therapies from reaching patients that need them.
Pg. 3 Para. 4	The endotoxin levels should be kept to less than 0.2EU/kg/dose/hour when the drug product is administered by the intrathecal route.	1. The Agency could consider removing the references to specific values, instead recommending that levels be kept as low as possible. If the specific levels are retained, the Agency may add a reference to USP general Chapter <85> (to the established limits of 10 ng/dose, if possible. The	1. Further clarity on rationale for proposed endotoxin limits and guidance to sponsors on justifications for endotoxin levels is needed.

		endotoxin levels should be kept to less than 0.2EU/kg/dose/hour when the drug product is administered by the intrathecal route). Moreover, FDA's draft guidance "Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biological Products" July 2020; provides for the following: "In the rare case that the combined endotoxin exposure exceeds the limits described above, sponsors should justify that such limits cannot be achieved based on specific aspects of product manufacturing and provide a rationale to support a conclusion that the risks to human subjects are reasonable considering the preliminary evidence of clinical activity of the investigational product, the seriousness of the disease, and the availability of satisfactory alternative therapies." Similar guidance should be included in the final GT for neurogenerative diseases guidance. 2. "The **drug product** endotoxin levels should be kept to less than 0.2EU/kg/dose/hour when the drug product is administered by the intrathecal route."	2. If limits are included, suggest clarifying that endotoxin limits are for drug product contribution only not cumulative endotoxin limit for drug product + device/companion diagnostic. Standalone delivery device limits are applied separately by CDRH.
Pg. 3 Para. 4	Lastly, plasmids can also be a source of process-related contaminants in adeno-associated virus (AAV)-based	If the plasmids are manufactured in a multi-product manufacturing facility, a risk assessment for the presence of another	Recommend to not limit the control of cross contamination to purely release testing of plasmids.

	GT products. Plasmids used to generate recombinant AAV-based products should be of the highest purity. If the plasmids are manufactured in a multi- product manufacturing facility, they should be tested for the presence of other contaminating plasmids that may have been co-purified.	contaminating plasmids that may have been co-purified, must be undertaken. And 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.** ~~**they should be tested for the presence of other contaminating plasmids that may have been co-purified.**~~	
Pg. 3. Para. 5	Drug product identity should be evaluated very early in product development. A consistent assay should be phased-appropriate qualified prior to the initiation of any studies designed to evaluate the product's suitability for use in a clinical investigation under an IND.	We recommend clarification of expectations for the initial IND submission and the material to be used in the clinical study.	Additional detail is necessary to inform proper execution of drug product identity evaluation.
Pg. 4 Para. 1	For products designed to treat neurodegenerative diseases, where the product may exhibit more than one mode of action, we encourage the evaluation of multiple product characteristics that could be used to establish a matrix or other similar approach to potency evaluation during initial clinical studies.	"For products designed to treat neurodegenerative diseases, where the product may exhibit more than one mode of action, we encourage the evaluation of multiple product characteristics ~~**that could be used to establish a matrix or other similar approach**~~ **be performed to inform** potency evaluation during initial clinical studies.	Multiple modes of action may not necessarily mean that a matrix approach to potency is needed.

Pg. 4 Para. 2	Drug product strength (e.g., vector genomes/mL) is a CQA that should be carefully measured and evaluated. This is especially crucial for GT vectors that may be expected to have sustained biological activity over the lifetime of the subject, including pediatric subjects. GT product strength should be evaluated with a well-qualified assay (Ref. 1).	1. Request the Agency provide additional considerations for timing for drug product strength as a CQA. 2. Suggested text change "GT product strength should be evaluated with a ~~**well-**~~ qualified assay (Ref. 1)." and request FDA provide additional detail on what constitutes a "qualified assay".	1. Additional specifics on appropriate development stages for product characterization will improve sponsor-FDA communications and avoid unnecessary delays in development. 2. Further guidance is necessary to inform sponsors developing assays for GT product strength.
Pg. 4 Para. 3	Sponsors should evaluate the effect of manufacturing process changes on the product's CQAs. In cases where the effect of product changes may not be immediately discernable, sponsors should be prepared to conduct a two-component risk analysis. One component of the risk analysis should be based on a prospective analysis of the effect of product changes using a side-by-side analysis of pre- and post-change product using multiple assay methods. The second component of the risk analysis should involve a retrospective analysis at a future date by preserving sufficient quantities of post-change product samples.	Sponsors should evaluate the effect of manufacturing process changes on the product's CQAs. In cases where the effect of product changes may not be immediately discernable, sponsors should be prepared to conduct a two-**step risk assessment** ~~**component risk analysis**~~. One component of the risk analysis should be based on a prospective analysis of the effect of product changes using a side-by-side analysis of pre- and post-change product using multiple assay methods. The second component of the risk analysis should involve a retrospective analysis at a future date by preserving sufficient quantities of post-change product samples.	FDA to clarify that the expectation is to have a second step for comparability which is retrospective in nature.

Pg. 4 Para. 5	If a sponsor plans to use a delivery device within the cleared or approved indications for use, compatibility of the investigational product with the delivery device should be demonstrated prior to initiating Phase 1 safety studies, as discussed above. If use of a delivery device falls outside the cleared or approved indications for use or if the delivery device has not been cleared or approved by the FDA for any indication, we recommend early discussion with FDA (see section VI of this document) to determine the additional information that may be needed to inform FDA's safety evaluation of the delivery device when used with the investigational product for the proposed clinical use.	Request further clarity on how sponsors can best address a disparity in device controls in the scenario where no, or limited, indicated products exist and specific use does not explicitly fall outside of the indication.	FDA has cleared or exempted several general-purpose devices (e.g., syringes) which may not be appropriate for use in specialized indications such as intrathecal or ophthalmic due to lack of specific controls (general purpose endotoxin controls for syringe = 20EU/device, ophthalmic controls = 0.2EU/device).
Pg. 5 Para. 5	Data derived from preclinical POC studies may guide the design of the preclinical toxicology studies, as well as the early-phase clinical trials. The animal species and/or models selected should demonstrate a biological response to the investigational GT product that is expected to be similar to the response in humans.	We request FDA provide additional clarification on the need for functional and/or behavioral phenotypes. Functional/behavioral endpoints should not be a required prerequisite for preclinical testing and inclusion should be at the discretion of the sponsor.	"Biological response" is interpreted as addressing pharmacodynamics only. Functional/behavioral phenotypes are noted later in the section and have been required for GT programs, clarification here would be beneficial.

Pg. 6 Para. 2	Biodistribution studies should be conducted to assess the distribution, persistence, and clearance of the vector and possibly the expressed transgene product, from the site of administration to target and non-target tissues, including applicable biofluids (e.g., blood and cerebrospinal fluid (CSF)), as feasible. These data can determine extent of tissue transduction and transgene expression, evaluate whether expression is transient or persistent, and guide the design of the preclinical toxicology studies as well as the early-phase clinical trials (Refs. 6, 7, and 8).	Language implies standalone biodistribution, however, suggest clarifying that these studies can be conducted with pharm/tox studies. Moreover, suggest for gene therapy serotypes administered via a clinically relevant ROA, the Agency provide recommendations on leveraging relevant preclinical/clinical biodistribution data in lieu of conducting additional biodistribution studies.	From a 3Rs perspective along with interpretation of distribution and persistence, definitive biodistribution studies can be conducted with pharm/tox studies.
Pg. 6 Para. 3	Toxicology studies for an investigational GT product should incorporate elements of the planned clinical trial (e.g., dose range, ROA, dosing schedule, and evaluation endpoints), to the extent feasible.	"Toxicology studies for an investigational GT product should incorporate elements of the planned clinical trial (e.g., **scaled** dose range, ROA, dosing schedule, and evaluation endpoints), to the extent feasible." Additional guidance on dose scaling from animal models to human would be welcome. For central administration, CSF volume for scaling is often desirable but accuracy can be a challenge for small animals, in these cases brain weight or body weight may be acceptable.	Current text only states 'when feasible', spelling out scaling provides a clear suggestion as to the how to do it. The best options for dose scaling depend on both the ROA (ICM/LP, IV, IT) and animal size. Further considerations on dose scaling based on brain weight, CSF volume, or body weight would be informative to sponsors developing toxicology study plans.
Pg. 6 Para. 4	However, due to differences in anatomy in rodents as compared to	1. It would be helpful for FDA to comment on the extent that toxicology assessment should	1. FDA generally encourages sponsors to obtain toxicology data

	the central and peripheral nervous systems in humans, animals with larger brains or spinal columns, such as pigs or nonhuman primates, may provide additional safety information and facilitate dose extrapolation	be, or not be, included in the rodent studies. When feasible, toxicology data should be collected in animal models when pharmacology is evaluated. 2. Suggest adding the following to the excerpt: "However, due to differences in anatomy **and genetics** in rodents as compared to the central and peripheral nervous systems in humans, animals with larger brains or spinal columns, such as pigs or nonhuman primates, may provide additional safety information and facilitate dose extrapolation." 3. "…with larger brains or spinal columns, such as pigs, **dogs,** or nonhuman primates, may provide additional safety information…"	in animal models when pharmacology is evaluated. Wild type littermates can also be used for safety assessments when the disease pathology interferes with assessment of toxicology endpoints. 2. The draft guidance does not cover different genetic backgrounds between rodents and humans. However, this can be important as working with surrogates might not be possible or sufficient (e.g., some animals do not express the gene, or the genetic sequences are not well conserved). For reduction of the target gene via shRNA it might be more appropriate to use human derived cellular models than with rodent systems.
Pg. 6 Para. 4	Inclusion of larger animals may also allow for the evaluation of the surgical dosing procedures and delivery device systems intended for clinical use (refer to section II of this document for additional discussion of delivery devices).	Request additional considerations for sponsors in selection of animal models to characterize different attributes (e.g., distribution/transduction rates, simulating dosing with deliver device, etc.)	The choice of biped or quadruped large animals can influence distribution of GT with different route of administration especially lumbar puncture (LP)/intra-cisterna magna (ICM). For instance, a larger animal may be necessary to simulate dosing (including volume and use of delivery devices), which may be limited to quadrupeds, and

			therefore need to be supplemented with smaller animal data and/or NHPs to characterize distribution within the CNS.
Pg. 5 Para. 5	Functional endpoints for POC studies in models of neurodegenerative disease often require neurobehavioral testing to demonstrate activity following administration of the investigational GT product. Adequate training of personnel, inclusion of appropriate controls, masked assessment of study endpoints, and use of well-defined scoring systems are recommended to avoid potential bias in these studies.	Including a discussion and potential alternatives in the guidance for scenarios when there are limitations in functional tests or limitations in the animal model at the functional level, but not molecular level, would be very informative. Additional in-line edit: "Adequate training of personnel, inclusion of appropriate controls **and testing room/environment**, masked assessment of study endpoints, and use of well-defined scoring systems are recommended to avoid potential bias in these studies."	Some disease models recapitulate the molecular pathogenesis of the disease but not the functional endpoints. Functional tests, especially in large animals (pigs and monkeys) can be challenging to collect and interpret. Testing room/environment can also impact the neurobehavioral data significantly.
Pg. 7 Para. 4	All subjects in trials of GT products for neurodegenerative diseases should receive the best standard of care, and no patient should be denied effective therapies in order to be randomized to a placebo-only arm.	"All subjects in trials of GT products for neurodegenerative diseases should receive ~~**the best standard of**~~ **appropriate** care, and no patient should be denied effective therapies in order to be randomized to a placebo-only arm."	This may not be feasible in instances where SOC would confound the results of the GT study (e.g., enzyme replacement therapy). The latter half of the sentence sufficiently conveys that where effective therapies are available, they should not be withheld.
Pg. 8 Para. 2	With the provisions above in mind, whenever possible FDA generally recommends that sponsors conduct	Considerations should be given for invasive/higher-risk routes/modes of delivery to the CNS where sham procedures are not	Sham procedures may introduce risks (e.g., exposure to anesthesia, incision site infection) in more

	randomized, concurrent-controlled (e.g., placebo, sham-procedure), double-blind clinical trials, even for first-in-human studies.	ethical and/or double-blinding is not feasible. Recommendations should acknowledge that GT products for neurodegenerative diseases are more likely to require such targeted but invasive delivery. In addition, consideration should be given to challenges associated with administration of prophylactic corticosteroids to subjects in a placebo-control or sham-control group.	invasive routes of CNS delivery or modes involving more invasive delivery devices (such as implanted).
Pg. 8 Para. 5	Even under these circumstances, however, historical controls may be inadequate (e.g., if important prognostic covariates either are unknown or were not recorded in the historical record) (Refs. 11 and 12). As a result, FDA generally does not encourage use of external, historical controls in place of a concurrent comparator group.	The following text could be added to the guidance. "**~~As a result, FDA generally does not encourage use of external, historical controls in place of a concurrent comparator group~~. FDA will consider use of historical controls, in place of or in addition to a concurrent comparator group when justified and depending on the relevance and robustness of historical control data. Using historical controls as part of the innovative trial design should be discussed with the FDA early in product development."**	The language for historical controls seems conflicting with regards to when/if historical controls may be considered.
Pg. 8 Para. 6	For clinical trials of GT products providing gene replacement, genetic diagnosis is essential for identifying potential clinical trial participants; presence of the genetic mutation should be confirmed prior to enrollment.	"… presence of genetic mutation or abnormal levels of gene product should be confirmed prior to enrollment**.**	Program specific consideration may be necessary when abnormalities in the gene product (i.e., protein levels) are more relevant to the diagnosis and laboratory tests are available to detect those abnormalities.

Pg. 9 Para. 1	If a reliable genetic diagnostic test is not readily available, a companion diagnostic may need to be developed to appropriately select subjects for the study. Similarly, sponsors may choose to exclude potential trial participants who demonstrate pre-existing antibodies to the GT product; in those cases, the sponsor should strongly consider development of a companion diagnostic to detect such antibodies.	1. Request clarification on expectations for the level of development necessary before selection of subjects versus marketing application. 2. Suggested edit, "...sponsors may choose to exclude potential trial participants who demonstrate pre-existing antibodies to **elements of** the GT product **(e.g., capsid, transgene).**	As written, text implies that a companion diagnostic would need to be fully developed (validated) prior to selecting subjects, which could lead to significant delays in study start.
Pg. 9 Para. 3	In general, eligibility for first-in-human GT trials should consider disease severity or stage as part of the benefit-risk profile. Further details on this topic are available in a separate guidance document (Ref. 9). If preliminary safety data support further clinical development, sponsors may then consider including a broader patient population in future trials.	1. Recommend clarifying whether populations can be expanded in a FIH study through additional cohorts in the same study. 2. Does the agency have a recommendation or feedback on risk/ benefit analysis when intervention in asymptomatic patients, and clinical outcome is delay of symptom onset?	The referenced guidance suggests general flexibility but additional considerations on use of same-study cohorts would be beneficial.
Pg. 10 Para. 2	FDA encourages substantial dose exploration throughout clinical development, to identify potentially safe and therapeutic dose(s) for a wide group of subjects. Doing so may be of heightened importance for some gene therapy products since	The guidance recommends completing dose-ranging study designs in early phase trials yet encourages substantial dose exploration throughout clinical development, with minimal examples for why substantial dose exploration throughout clinical development is beneficial (e.g., different stage of disease).	Although dose exploration can be completed throughout clinical development, dose range exploration studies are often completed in early clinical development to determine the tolerability of the dose range

	subjects may have only one chance to receive the product: stimulation of antibodies and T-cell immune responses to the product may preclude repeat administration.	For GT products there are concerns of trying to reduce exposure of non- efficacious doses to as few patients as possible. In addition, given that subjects may only have one chance to receive the product, the guidance should comment that the study treatment should ideally start with a potentially therapeutic dose. Additional information could be provided for how to complete dose exploration studies in ultrarare diseases	expected to be evaluated in later clinical studies.
Pg. 10 Para. 6	Immune responses to GT products may pose important safety risks, such as by damaging the tissues transduced by viral vectors carrying a therapeutic transgene. To monitor for systemic immune reactions, sponsors should perform immunoassays measuring cellular and humoral immune responses to both the vector and the transgene-encoded protein.	"… sponsors should perform immunoassays measuring cellular and**/or** humoral immune responses to both the vector and the transgene-encoded protein **as needed**."	Whereas detection of cellular responses is of potential clinical value, the assays used to assess that parameter tend to be less sensitive and less robust. In multiple contexts, detection of a humoral immune response may provide a reliable marker for drug-vector related safety considerations.
Pg. 10 Para. 4	Invasive surgical procedures may be necessary to administer a GT product (e.g., intracranial delivery to a targeted region of the brain or spinal cord). In such cases, FDA recommends that the sponsor utilize a staged approach: initiating the early-phase study with unilateral administration, and if no significant	1. "Invasive surgical procedures may be necessary to administer a GT product (e.g., intracranial delivery to a targeted region of the brain or spinal cord). In such cases, **sponsors should consider any necessary risk mitigations in planning dose administration, such as ~~FDA recommends that the sponsor utilize a staged approach~~**: initiating the early-phase study with **sentinel group dosing**, and	Unilateral administration is not always clinically supported. Even when feasible to perform unilateral administration, it is unlikely to lead to therapeutic benefit. Precisely because these are invasive surgical procedures, subject should not be required to undergo multiple procedures. This should not be the

	safety concerns arise, then proceeding to bilateral administration of the GT product.	if no significant safety concerns arise, then proceeding **~~to bilateral~~ with further cohort** administration of the GT product.**"** 2. Additional guidance would be welcome with regards to 1) ensuring the initial dose has therapeutic potential, which may be difficult to achieve when half the dose is administered via unilateral administration), and 2) how to analyze data from subjects that receive unilateral administration. FDA should consider providing guidance on unilateral and bilateral delivery in nonclinical studies, and potentially switching to bilateral administration during early-phase studies if no significant safety concerns arise	default approach for invasive procedures and should be considered on a case-by-case basis as justified by the safety data from appropriate preclinical models and relevant clinical studies. FDA should provide more detail and acknowledge that repeat administration of some GT products or drugs may not be possible due to the immune response.
Pg. 11	Study Endpoints Section	We suggest that FDA clarify their definition of 'clinical benefit' with a reference to 'how patients feel, function and survive' and explicitly state that clinical benefit can be assessed using patient-focused outcomes, such as patient reported outcomes (PROs). Citation for clinical benefit definition: https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-C	We suggest FDA explicitly state that clinical benefit can be assessed by clinical outcome assessments (COAs) including PROs, ClinROs, ObsROs, PerfOs, and passive monitoring outcome assessments). Certain types of COAs may be viewed as less important as they are more subjective. However, they are critical tools to assess how patients feel or function, which may just as or more important to patients than

			more traditional clinical outcomes such as survival.
Pg. 11 Para. 2	Clinical endpoints should enable assessment of potential clinical benefit; biomarkers and potential surrogate endpoints may indicate activity of the GT product. Such endpoint assessments may help guide further clinical development. For example, changes in the amount of transgene product expressed in the targeted tissue may provide early evidence of GT product activity and thus inform subsequent dose selection.	Conventional approaches to demonstrating change in the level of transgene product include the presence of transgene mRNA, protein levels or other biomarkers of therapeutic activity. However, conventional approaches may not be appropriate where CNS is the target tissue in measuring transgene product expression. What is the Agency's current thinking on identification and use of peripheral biomarkers for safety and efficacy monitoring?	There are challenges in measuring transgene expression using conventional methods in CNS diseases. Additional FDA guidance on alternative forms of early evidence that might be indicative of product activity and help to inform dose selection would be welcome.
Pg. 11 Para. 1	To minimize immune responses, immunosuppressant drugs such as corticosteroids may be utilized before and after product administration. Sponsors should provide justification for the immunosuppressant regimen, based on available clinical data for the investigational product or related products.	1. Request further detail on the Agency's view of open label versus blinding in cases of required immunosuppression. 2. Information on how to pragmatically implement providing justification for the immunosuppressant regimen should be provided in the guidance.	1. Immunosuppression carries risks but to maintain blinding all subjects may be required to receive it. 2. Additional guidance on implementation is needed as the regimen will vary depending on a product, target/tissue of interest/tropism of viral vector, type of transgene being expressed (secreted, transmembrane, intracellular), stage of disease, circumstances for immunosuppressant administration (prophylactic vs reactive

			immunosuppressant regimen) and subjects baseline antibody status.
Pg. 11 Para. 5	When a suitable surrogate endpoint is identified, it may be used to support a marketing application under the accelerated approval pathway. Use of a surrogate endpoint may be appropriate when a GT product directly targets an underlying, well-understood and well-documented monogenic change that causes a serious neurodegenerative disorder. In these cases, the GT product could alter the underlying genetic defect and thereby treat or cure the disease.	"Use of a surrogate endpoint may be appropriate when a GT product directly targets an underlying, well-understood and well-documented ~~**monogenic**~~ **genetic** change that causes a serious neurodegenerative disorder."	If underlying disease biology and pathogenesis is well understood, it is not necessary for this to only apply to monogenic diseases. This unnecessarily limits application of accelerated approval for GT products.
Pg. 12 Para. 2	Patient experience data[5] may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application.	1. "FDA encourages sponsors to collect patient experience data **(e.g., qualitative or quantitative data to highlight patient perspective on benefit risk and the relative importance of treatment characteristics)** during product development, and to submit such data in the marketing application." 2. Suggest the footnote be expanded to also include "patient input on which outcomes are important to them and the relative importance of any issue as defined by patients".	We appreciate FDA affirming that PED is important to inform benefit risk. Sponsors are seeing a number of discrete choice experiments in patient preference taking off for specific diseases and suggest the additional detail be considered for the final guidance