

Human Gene Therapy for Neurodegenerative Diseases

Guidance for Industry

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance provides recommendations to sponsors developing human gene therapy (GT) products¹ for neurodegenerative diseases affecting adult and pediatric patients. Neurodegenerative diseases are a heterogeneous group of disorders characterized by progressive degeneration of the structure and function of the central nervous system or peripheral nervous system. These diseases vary in etiology, prevalence, diagnosis, and management, and include genetic as well as age-related diseases.² This guidance focuses on considerations for product development, preclinical testing, and clinical trial design. This guidance finalizes the draft guidance of the same title dated January 2021.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

¹ Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), <https://www.fda.gov/media/76647/download>).

² The principles in this guidance may also apply to GT products for other types of neurological diseases, including neurodevelopmental disorders.

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II. CONSIDERATIONS FOR CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

Treatment of neurodegenerative diseases may include the use of GT products, such as viral vectors, that have tropism to neuronal tissue to contribute to treatment effect. The general CMC considerations for product manufacturing, testing and release of GT products for neurodegenerative diseases are the same as those described for other GT products (Ref. 1). However, some aspects of GT products for neurodegenerative diseases, such as challenges associated with the route of administration, volume of product that can be administered, the delivery device, and the study population size, may involve additional CMC considerations.³

Typically, critical quality attributes (CQAs) of an investigational drug product are evaluated during each phase of clinical development, and characterization data from multiple drug product lots are correlated to clinical outcomes. Early-phase clinical studies of neurodegenerative diseases involving small study populations, in addition to focusing on safety assessments, may also provide early evidence on effectiveness. In cases where early-phase clinical studies are used to provide evidence of effectiveness to support a marketing application, the product's CQAs and manufacturing critical process parameters (CPPs) should be thoroughly evaluated and appropriate controls implemented during the early clinical development phase. In addition, innovative manufacturing strategies such as the production of multiple small lots versus a single large product lot may be considered to increase manufacturing process experience and product knowledge (Ref. 2). GT products may have quality attributes with higher variability than small molecule drugs or well-characterized biological products, and sponsors should consider additional product characterization studies to establish acceptance limits for the CQAs. For licensure, it is important to demonstrate process control to ensure a consistent product with predefined CQAs for product strength (e.g., vector genomes/mL), potency, identity, and purity (Refs. 1 and 3). Products used to treat neurodegenerative diseases may have to be administered in small volumes to sites of the disease or condition, 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. Product CQAs may also influence the final formulation parameters, and decisions regarding these product aspects may need to be made early in the manufacturing process development. Therefore, we recommend that assays for evaluating product quality attributes be implemented early in product development and qualified as suitable (i.e., accurate, precise, sensitive, and specific).

Sponsors developing GT products for neurodegenerative diseases are strongly encouraged to contact the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) (refer to section VI of this document) prior to submitting an investigational new drug application (IND) (21 CFR Part 312) and during product development to discuss their product-specific considerations, which may include:

³ This guidance is not designed to be a stand-alone guidance on CMC considerations for GT products for neurodegenerative disorders. Sponsors also should refer to the general CMC guidance documents on cell and gene therapies available from the FDA's web site: <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>.

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- Design of GT products should be based on current scientific knowledge and an evaluation of potential risks posed by the product to study subjects. GT products may induce unintended 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, damage to the host cells, and environmental shedding. We recommend that all GT products for neurodegenerative diseases be designed to reduce unintended immune responses, reduce the possibility of becoming latent, and not contain foreign genes that do not directly contribute to the biological function of the investigational product (e.g., reporter genes).
- 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).
 - 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 qualified assays for evaluation of empty particles (where applicable), product-related variants (mutations in the viral genome, transgene, etc.), and non-recombinant viral particles (e.g., replication-competent viruses, wild-type viruses) be established early in the product development cycle.
 - 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. Depending on the location of product administration and the expected low 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 sponsors carefully consider characteristics of the cell lines used in the manufacture of viral vectors that may impact the safety of the final product (such as presence of tumorigenic sequences) and limit residual host cell-DNA levels and DNA size. For additional information, refer to the CMC guidance (Ref. 1). The endotoxin levels should be kept to less than 0.2EU/kg body weight/hour when the drug product is administered by the intrathecal route. Lastly, plasmids can also be a source of process-related contaminants in viral vector (e.g., adeno-associated virus (AAV))-based GT products. Plasmids used to generate recombinant viral vectors should meet acceptable limits for purity, and manufacturing controls should be in place to avoid cross-contamination of plasmids. 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. Alternatively, a risk assessment may be conducted to provide assurance of freedom from other contaminating plasmids that may have been co-purified.

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- Drug product identity should be established prior to the initiation of any nonclinical studies designed to evaluate the product's suitability for use in a clinical investigation under an IND. For additional information, refer to the CMC guidance (Ref. 1).
- Drug product potency assays are critical to assess the product's functional activity, consistency, and stability, and to provide evidence of comparability after changes to the manufacturing process (Refs. 4 and 5). 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. We recommend that a potency test (Ref. 6) that measures relevant biological activities be qualified for suitability (i.e., accuracy, precision, sensitivity, specificity) prior to conducting clinical trials intended to provide substantial evidence of effectiveness to support a marketing application. The potency test should be validated prior to submitting a biologics license application (BLA) under section 351 of the PHS Act and 21 CFR 601.2.
- Drug product strength 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 an assay qualified as suitable (i.e., accurate, precise, sensitive, and specific) prior to initiating clinical studies (Ref. 1).
- Sponsors should evaluate the effect of manufacturing process changes on the product's CQAs. Sponsors should be prepared to conduct a risk analysis and, if necessary, a comparability study. The risk analysis should be based on a prospective analysis of the potential effects of process changes using a side-by-side analysis of the product pre- and post-change. Sponsors should discuss comparability protocols and changes to the manufacturing plans with FDA prior to implementing changes. The extent of comparability studies should depend on the manufacturing change, the ability of analytical methods to detect changes in the product, and the stage of clinical development. After discussing the proposed comparability protocol and manufacturing changes with FDA, sponsors should be prepared to perform the comparability study. It is critical that sufficient samples are retained (such as in-process materials, drug substance (DS), DS intermediates, and drug product (DP)). After the comparability study is conducted, sponsors should submit the data from the comparability studies as an amendment to the IND (21 CFR 312.31(a)(1)) for FDA review prior to implementing the change for investigational use in clinical studies. For general recommendations on the design of comparability studies, sponsors may refer to the FDA comparability guidance (Ref. 4) and the International Council for Harmonisation (ICH) Q5E document (Ref. 5). Sponsors are also encouraged to consider, where possible, implementing manufacturing changes needed for commercial-scale production and demonstrating product comparability prior to the initiation of clinical trials intended to provide substantial evidence of effectiveness to support a marketing application. Importantly, if product comparability cannot be demonstrated, additional clinical studies may be needed to support BLA approval.

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- When a device is used to deliver the investigational product, compatibility of the product with the delivery device (e.g., no loss of strength or potency, no increase in impurities, etc. of the investigational product after passing through the delivery device) should be demonstrated prior to initiating Phase 1 safety studies (21 CFR 312.23(a)(10)(iv) and 21 CFR 312.23(a)(11)). Such studies should be carried out with the final formulated investigational product that is intended to be used in the clinical study, under conditions that would mimic those planned in the clinical study. Specifically, the delivery device, product concentration (tested over the planned dose-range), drug product formulation, final infusion volume, duration and rate of infusion, and temperature for the device compatibility studies should be representative of what will be used in the clinical study.
- 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 study.
- FDA encourages sponsors to discuss pharmaceutical quality development plans early, such as at the pre-investigational new drug application (pre-IND) meeting, and throughout the drug development process. This continuous engagement with the Agency can decrease the potential for developmental or approval delays related to manufacturing changes introduced at various stages in the product's life cycle.

III. CONSIDERATIONS FOR PRECLINICAL STUDIES

A preclinical program that is tailored to the investigational product and planned early-phase clinical trial contributes to characterization of the product's benefit/risk profile for the intended patient population. The overall objectives of a preclinical program for a GT product include: 1) identification of a biologically active dose range; 2) recommendations for an initial clinical dose level, dose-escalation schedule, and dosing regimen; 3) establishment of the rationale for, and reasonable safety of, the proposed clinical route of administration (ROA); 4) support of patient eligibility criteria; and 5) identification of potential toxicities and physiologic parameters that help guide clinical monitoring for a particular investigational product. It is also important to provide scientific support for the method of dose level extrapolation between animals and humans. In addition, to justify conducting a pediatric first-in-human clinical trial that is associated with more than a minor increase over minimal risk, the preclinical program should include studies designed to demonstrate a prospect of direct benefit (21 CFR 50.52) of the investigational GT product (refer to section IV.B. of this document for further discussion). Preclinical evidence to support a prospect of direct benefit is most important when clinical evidence of effectiveness is not available from adult subjects with the same disease.

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Further details for general considerations in preclinical studies of these investigational GT products are available in a separate guidance document (Ref. 7). The following elements are recommended in the development of a preclinical program for an investigational GT product intended for treatment of a neurodegenerative disease:

- Preclinical in vitro and in vivo proof-of-concept (POC) studies to establish feasibility and to support the scientific rationale for administration of the investigational GT product in a clinical trial should be considered. Data derived from preclinical POC studies may guide the design of the preclinical toxicology studies, as well as the early-phase clinical trials. Animal models of neurodegenerative disorders are often used to generate POC data. Such models may provide the opportunity for identification of disease-relevant risks and biomarkers of activity that may be applicable for monitoring in 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.⁴
- 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. 7, 8, and 9).
- Toxicology studies for an investigational GT product can be conducted in animal models of neurodegenerative disease, as well as in healthy animals, as appropriate. Study designs should incorporate elements of the planned clinical trial (e.g., dose range, ROA, dosing schedule, and evaluation endpoints), to the extent feasible. Study designs should be sufficiently comprehensive to permit identification, characterization, and quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed) and potential mitigation and/or resolution, and the effect of dose level on these findings. In some cases, additional assessments may also be important to consider, such as clinical neurological evaluations, neuropathology, and the immune response directed against the vector and the expressed transgene product. In addition, for any significant abnormal findings or lesions, sponsors should determine the frequency, severity, potential cause, and possible clinical significance.
- Due to differences in anatomy 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

⁴ The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VI of this document). We would consider whether such an alternative method could be used in place of an animal test method.

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extrapolation. 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). Scientific justification should be provided to support selection of animal models. These animal models, and their justification, will be evaluated by the FDA in the context of each investigational GT product and proposed clinical indication.

- 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.
- Evaluation of the potential for developmental and reproductive toxicity may be warranted, depending on such factors as the vector construct, the expressed transgene product, biodistribution data, and the target clinical population. If significant changes in the manufacturing process or product formulation occur during product development which may impact comparability between the product administered in clinical trials and the product intended for licensure, the conduct of additional pharmacology/toxicology studies should be considered.

IV. CONSIDERATIONS FOR CLINICAL TRIALS

The fundamental considerations for clinical development programs of GT products for neurodegenerative diseases are similar to those considerations for other biological products, as detailed in relevant FDA guidance documents (Refs. 10 and 11). The following are general recommendations regarding development of clinical programs of investigational GT products for neurodegenerative diseases.

FDA recognizes that neurodegenerative diseases constitute a heterogeneous group of disorders. Some neurodegenerative diseases are monogenic disorders with relatively well-characterized pathogenesis and pathophysiology (e.g., infantile spinal muscular atrophy due to mutations in the *survival motor neuron 1* gene). When the natural history of such monogenic disorders is also well-characterized and relatively consistent (i.e., not highly variable), and when the expected clinically meaningful treatment effect is large, self-evident, and closely associated temporally with the intervention, innovative clinical trial designs, rather than randomized, placebo-controlled trials, may be feasible to expedite clinical development. In contrast, many other neurodegenerative disorders have a poorly understood etiology and/or pathophysiology, with a poorly characterized or highly variable natural history (e.g., sporadic amyotrophic lateral sclerosis or sporadic Alzheimer's disease). For these disorders, randomized, concurrent-controlled (e.g., placebo, sham-procedure) clinical trials with appropriate blinding may be the most efficient means of obtaining persuasive evidence of effectiveness. For any neurodegenerative disorder, regardless of etiology, pathophysiology, and natural history, sponsors are encouraged to consider whether innovative trial designs (e.g., adaptive designs, enrichment designs, dose-controlled studies, or historical controls) both may be justified and may

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facilitate product development. In all cases, however, to promote product development, we encourage sponsors to discuss clinical development plans with FDA early in product development.

A. Study Design

- 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. 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. For studies involving placebo, FDA recommends add-on designs, in which a treatment previously shown to be effective for the neurodegenerative condition is given to all subjects participating in the trial, with subjects then randomized to receive the added GT product or added placebo.
- With the provisions above in mind, whenever possible FDA generally recommends that sponsors conduct randomized, concurrent-controlled (e.g., placebo, sham-procedure), double-blind clinical trials, even for first-in-human studies. Such randomized designs best facilitate interpretation of clinical data and can be the most efficient way to demonstrate safety and effectiveness of GT products. For conditions where the disease course is well-characterized, highly predictable, and can be objectively measured and verified (e.g., temporally predictable mortality), randomized studies potentially may not be needed, especially if the clinically meaningful treatment effect is large and such improvement would not be expected without treatment.
- Sponsors developing a GT product for a rare neurodegenerative disease should consider designing their first-in-human study to be an adequate and well-controlled investigation so that the results of such a study may provide evidence of effectiveness to support a marketing application. Even though first-in-human studies may have limited power to detect differences in effectiveness, the design elements, such as randomization, concurrent-control, blinding, and use of clinically meaningful efficacy endpoints, enhance interpretability of preliminary safety and efficacy data to guide further clinical development.
- When appropriate, crossover designs may also be considered in concurrent-controlled trials to allow patients in the control group to receive the GT product after completion of the randomized, controlled portion of the trial. To allow for additional prespecified effectiveness assessments, we recommend that during the open label extension period, patients, investigators, site personnel, and site monitors remain blinded to treatment group assignment from the randomized treatment period.

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- For trials using a sham procedure as the concurrent control, FDA recommends the sham procedure be as minimally invasive as possible while still maintaining blinding of appropriate parties (e.g., evaluators, study patients, and families).⁵
- Trials using external controls (e.g., a natural history control) rather than a concurrent comparator group to which a suitable fraction of enrolled subjects are randomized for comparison may be appropriate under certain circumstances, such as with a GT product intended to treat a rare and serious neurodegenerative disease for which (1) there is an unmet medical need; (2) inclusion of a concurrent control is not practical or ethical; (3) the disease course is well-documented, highly predictable, and can be objectively measured and verified, such as high and temporally predictable mortality; (4) the study population and the external controls are suitably comparable; and (5) the expected treatment effect is large, self-evident, and closely associated temporally with the intervention. Even under these circumstances, however, external controls may be inadequate (e.g., if important prognostic covariates either are unknown or were not recorded in the historical record) (Refs. 12 and 13). As a result, FDA generally does not encourage use of external controls in place of a concurrent comparator group.

B. Study Population

- For clinical trials of GT products for treatment of a neurodegenerative disorder due to mutation(s) in a gene, genetic diagnosis is essential for identifying potential clinical trial participants; presence of the genetic mutation should be confirmed prior to enrollment. 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.
- Sponsors may choose to exclude potential trial participants who have pre-existing antibodies to elements of the GT product (e.g., capsid, transgene) above certain level(s) justified by scientific data. In those cases, the sponsor should strongly consider development of a companion diagnostic to reliably detect such antibodies.
- Early in product development, sponsors should communicate with the Agency about the possible need for companion diagnostics and the proper development pathway (e.g., the study risk determination and the need for an Investigational Device Exemption application). If an in vitro companion diagnostic is needed to appropriately select subjects for a study (and later for treatment, once the GT product is approved), the sponsor should coordinate submission of the marketing application for the companion diagnostic with submission of the BLA for the GT product, to support contemporaneous marketing authorizations (Refs. 14 and 15).

⁵ See also Guidance for Industry: ICH E10 Choice of Control Group and Related Issues in Clinical Trials, May 2001; <https://www.fda.gov/media/71349/download>; and <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.

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- 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. 10). If preliminary safety data support further clinical development, sponsors are encouraged to then include a broader patient population in future trials.
- Certain neurodegenerative diseases affect adults as well as children. Sponsors who are developing GT products for these diseases should consider the following:
 - Whenever feasible, the first-in-human trial should be initiated in adult subjects who are able to understand the risks, and to provide informed consent. Sponsors should obtain preliminary safety and tolerability data (and in some situations, data to support preliminary effectiveness or substantial evidence of effectiveness) in adult subjects prior to beginning studies in pediatric subjects.
 - When no prior human safety or efficacy data are available, sponsors planning to conduct first-in-human trials in pediatric subjects should provide a rationale as to why adult studies are either not feasible or not ethical.
 - It is important that clinical investigations in pediatric subjects address ethical considerations for conducting investigations in vulnerable populations. FDA regulations at 21 CFR Part 50, Subpart D contain additional safeguards for children in clinical investigations. Clinical investigations involving no greater than minimal risk may involve children in accordance with 21 CFR 50.51. Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects may involve children as set forth in 21 CFR 50.52. An investigation involving greater than minimal risk and no prospect of direct benefit to individual subjects, but which is likely to yield generalizable knowledge about the disorder or condition, may involve children as set forth in 21 CFR 50.53, which includes, for example, a finding by the IRB that the risk represents a minor increase over minimal risk. FDA's regulation at 21 CFR 50.54 also addresses clinical investigations not otherwise approvable and describes a process to follow to determine whether the investigation may involve children. In addition to the determinations required under applicable provisions of Subpart D described above, adequate provisions must be made to obtain the permission of the parents and the assent of the child as described in 21 CFR 50.55.

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C. Dose Selection

- For early-phase trials of GT products, dose-ranging study designs are recommended. 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 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 these products, the clinical study should start with a likely therapeutic dose.
- The choice of an initial dose and dose regimen should be supported by preclinical studies and/or available clinical information. Such data should indicate that the initial dose not only is reasonably safe, but also has therapeutic potential, particularly when the procedure for administering the product carries substantial risks, or when the product will be administered to children.
- 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 use a staged approach: initiating the early-phase study with unilateral administration in a reasonable number of subjects, and if no significant safety concerns related to product administration arise, then proceeding to bilateral administration of the GT product in the early-phase study.
- To ensure consistency across study sites, sponsors should include in the study protocol a detailed description of both the product delivery procedure and the devices used for delivery.

D. Safety Considerations

- 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.
- To minimize immune responses, immunosuppressant treatments (e.g., corticosteroids) may be used 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. Because immunosuppressant drugs may cause adverse events, subjects should be closely monitored and treated, as necessary, to minimize the risk of complications.

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E. Study Endpoints

- FDA encourages sponsors to explore a wide range of endpoints to assess preliminary safety, activity and efficacy of a GT product in early-phase trials. Clinical endpoints should enable assessment of potential clinical benefit; biomarkers and potential surrogate endpoints⁶ may indicate activity of the GT product. Such endpoint assessments may help guide further clinical development.
- In trials intended to provide evidence of effectiveness to support a marketing application, primary efficacy endpoints should be either clinically meaningful endpoints that directly measure a clinical benefit, or surrogate endpoints that are reasonably likely to predict a clinical benefit.

Because many neurodegenerative diseases are rare and complex, with limited understanding of their pathogenesis, identification and characterization of a surrogate or intermediate endpoint is often challenging. Therefore, an effect on a clinically meaningful endpoint generally would be used to support a marketing application under the traditional approval pathway.

- When a suitable surrogate endpoint is identified, it may be used to support a marketing application under the accelerated approval pathway.⁷ Use of a surrogate endpoint may be appropriate under certain circumstances, such as 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.

Sponsors proposing to develop surrogate endpoint(s) to support accelerated approval should communicate with the Agency early in product development, preferably well before initiating clinical trials. Further information on the accelerated approval pathway is available in separate guidance documents (Refs. 16 and 17).

F. Follow-Up Duration

The length of follow-up necessary to provide sufficient information regarding the safety and efficacy of the GT product depends on many aspects of a GT product, including vector persistence, genome integration, and transgene activity, and the

⁶ According to section 507(e)(9) of the Federal Food, Drug, and Cosmetic Act (FD&C) Act [21 U.S.C. 357(e)(9)] “[t]he term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—

(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or

(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with Section 506(c).”

⁷ Further information on the accelerated approval pathway is available in separate guidance documents (Refs. 16 and 17).

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goal of the follow-up (e.g., safety vs. durability of clinical effect). In addition to monitoring for safety, long-term follow-up is recommended to evaluate durability of the clinical effect. More detailed discussion of long-term follow-up is provided in a separate FDA guidance document (Ref. 8).

G. Patient Experience

Patient experience data⁸ 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.

V. EXPEDITED PROGRAMS

There are several programs available to sponsors of GT products intended to address unmet medical needs in the treatment of serious or life-threatening conditions. These programs, including regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review, are intended to facilitate and expedite development and review of such therapies. In particular, regenerative medicine advanced therapy designation and breakthrough therapy designation call for increased FDA attention to these potentially promising therapies, offering sponsors more-frequent interactions with FDA on efficient trial design and overall drug development. Further information on these expedited programs is available in separate guidance documents (Refs. 16 and 17).

⁸ As defined in section 569C(c) of the FD&C Act, the term “patient experience data” includes data that are:

- Collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and
- Intended to provide information about patients’ experiences with a disease or condition, including the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy or clinical investigation, on patients’ lives; and patient preferences with respect to treatment of such disease or condition.

Additional information on Patient-Focused Drug Development can be found on this website:

<https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development> and on: <https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/center-biologics-evaluation-and-research-patient-engagement-program>.

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VI. COMMUNICATION WITH FDA

FDA encourages communication with OTAT early in product development, before submission of an IND. Different meeting types are available, depending on the stage of product development and the issues to be considered. These include pre-IND meetings and, earlier in development, Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT) meetings.⁹ Early, nonbinding regulatory advice can be obtained from OTAT through an INTERACT meeting, which can be used to discuss issues such as a product's early preclinical program, and/or through a pre-IND meeting prior to submission of the IND (Ref. 18).

⁹ For additional information about INTERACT meetings, please see <https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings>

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VII. REFERENCES

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Contains Nonbinding Recommendations

*When finalized, this guidance will represent FDA's current thinking on this topic.