

Human Gene Therapy for Retinal Disorders

Draft Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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I. INTRODUCTION

This guidance provides recommendations to stakeholders developing human gene therapy (GT) products¹ for retinal disorders affecting adult and pediatric patients. These disorders vary in etiology, prevalence, diagnosis, and management, and include genetic as well as age-related diseases. These disorders manifest with central or peripheral visual impairment and often with progressive visual loss. This guidance focuses on issues specific to GT products for retinal disorders and provides recommendations related to product development, preclinical testing, and clinical trial design for such GT products.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA’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 FDA’s 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. Human gene therapy products are defined as 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, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, (Ref.1) 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.

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32 **II. CONSIDERATIONS FOR PRODUCT DEVELOPMENT**

33
34 There are multiple GT products being studied in clinical trials in the United States for retinal
35 disorders. GT products are commonly delivered by intravitreal or subretinal injections through a
36 medical delivery system. In some cases, the GT products are encapsulated in a device to be
37 implanted intravitreally.

38
39 The general chemistry, manufacturing and control (CMC) considerations for product
40 manufacturing, testing and release of GT products for retinal disorders are the same as those
41 described for other GT products (Ref. 2). For early-phase clinical trials, a sponsor should be
42 able to evaluate the identity, purity, quality, dose, and safety of a GT product. A potency assay
43 to assess the biological activity of the final product, with relevant lot release specifications,
44 should be established prior to the initiation of clinical trials intended to provide substantial
45 evidence of effectiveness for a marketing application. To support licensure of a GT product,
46 manufacturing processes and all testing methods for product release must be validated
47 (21 CFR 211.165(e)). Sponsors developing GT products for retinal disorders are strongly
48 encouraged to contact the Office of Tissues and Advanced Therapies in the Center for Biologics
49 Evaluation and Research (CBER) early in product development to discuss product-specific
50 issues.

51
52 Sponsors of GT products for retinal disorders should take into account general CMC
53 considerations for all GT products (Ref. 2), as well as CMC considerations specific to the
54 products intended for treatment of retinal disorders, including:

- 55
- 56 • Consideration of the final product formulation and concentration to meet the expected
57 dose and volume requirement;
 - 58
 - 59 • The endotoxin limit for intraocular delivery is not more than (NMT) 2.0 Endotoxin Unit
60 (EU)/dose/eye or NMT 0.5 EU/mL (USP <771>);
 - 61
 - 62 • GT vector-based final products should be tested for particulate matter, and the test
63 method and release criteria should follow USP <789>;
 - 64
 - 65 • Product testing and release should include testing of the final product configuration;
 - 66
 - 67 • Compatibility of the GT product and the delivery system should be evaluated.
- 68

69 70 **III. CONSIDERATIONS FOR PRECLINICAL STUDIES**

71
72 A preclinical program that is tailored to the investigational product and the planned early-phase
73 clinical trials helps characterize the product's benefit/risk profile for the intended patient
74 population. Overall objectives of the preclinical program for a GT product include: 1)
75 identification of a biologically active dose level range; 2) recommendations for an initial clinical
76 dose level, dose-escalation schedule, and dosing regimen; 3) establishment of feasibility and

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77 reasonable safety of the proposed clinical route of administration (ROA); 4) support of patient
78 eligibility criteria; and, 5) identification of potential toxicities and physiologic parameters that
79 help guide clinical monitoring.

80
81 Further details for general considerations in preclinical studies of these investigational GT
82 products are available in a separate guidance document.² The following elements are
83 recommended for consideration when developing a preclinical program for an investigational GT
84 product intended for treatment of retinal disorders (some of which are not necessarily exclusive
85 to GT products for retinal disorders):

- 86
- 87 • Preclinical in vitro and in vivo proof-of-concept (POC) studies are recommended to
88 establish feasibility and support the scientific rationale for administration of the
89 investigational GT product in a clinical trial. Data derived from preclinical POC studies
90 may guide the design of both the preclinical toxicology studies, as well as the early-phase
91 clinical trials. The animal species and/or models selected should demonstrate a biological
92 response to the investigational GT product that is similar to the expected response in
93 humans.
 - 94
 - 95 • Biodistribution studies should be conducted to assess the pharmacokinetic profile of a GT
96 product (Ref. 3). These data encompass the distribution, persistence, and clearance of the
97 vector and possibly the expressed transgene product in vivo, from the site of
98 administration to target ocular and non-ocular tissues, intraocular fluids, and blood.
99 These data can determine extent of tissue transduction and transgene expression, evaluate
100 whether expression is transient or persistent, and guide the design of the preclinical
101 toxicology studies as well as the early-phase clinical trials.
 - 102
 - 103 • Toxicology studies for an investigational GT product should incorporate elements of the
104 planned clinical trial (e.g., dose range, ROA, dosing schedule, and evaluation endpoints,
105 etc.), to the extent feasible. Study designs should be sufficiently comprehensive to permit
106 identification, characterization, and quantification of potential local and systemic
107 toxicities, their onset (i.e., acute or delayed) and potential resolution, and the effect of
108 dose level on these findings. For any abnormal ophthalmic findings or lesions, sponsors
109 should determine the frequency, severity, potential cause, and clinical significance.
110 Inflammatory or immune responses should be further characterized to assess potential
111 attribution to the vector or transgene.
 - 112
 - 113 • Animal models of retinal disorders are frequently developed in rat or mouse strains (e.g.,
114 transgenic or knockout models) and these models are often utilized to generate POC

² Preclinical Assessment of Investigational Cellular and Gene Therapy Products; Guidance for Industry, dated November 2013, <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf>

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115 data.³ However, due to differences in ocular size and anatomy in rodents as compared to
116 the human eye, animals with more ‘human-like’ eyes, such as rabbits, pigs, dogs, or
117 nonhuman primates, may also provide applicable safety information. Inclusion of the
118 larger animals also facilitates relevant experience with the surgical procedures and
119 delivery systems intended for clinical use.

- 120
121 • Differences between the immune responses of animals and humans are important
122 considerations when interpreting preclinical data. Retinal disorders typically are bilateral
123 and chronic. However, a second administration of a GT product to either the
124 contralateral eye or to the same eye may not be feasible due to an immunologic reaction
125 against the vector and/or the transgene product. Therefore, clinical data, rather than
126 preclinical data, may provide the most relevant safety information for repeat product
127 administration.
- 128
129 • As the clinical development program for an investigational GT product advances to late-
130 phase clinical trials and possible marketing approval, additional preclinical studies may
131 be indicated. Further testing may be necessary to address factors such as any significant
132 changes in the manufacturing process or formulation, which may affect comparability of
133 the late-phase product to product administered in early-phase clinical trials.

136 IV. CONSIDERATIONS FOR CLINICAL TRIALS

137
138 The fundamental considerations for clinical development programs of GT products for retinal
139 disorders are similar to those for other biological products. Early-phase trials of GT products
140 should not only evaluate safety and feasibility, but also gauge bioactivity and preliminary
141 efficacy. Later-phase trials should be designed as adequate and well-controlled studies that can
142 provide substantial evidence of effectiveness to support an application for marketing. For further
143 details of general considerations for gene therapy clinical trials, please refer to relevant FDA
144 guidance documents.^{4,5}

145
146 The following important elements are recommended for consideration during development of
147 clinical programs of investigational GT products intended for treatment of retinal disorders.

³ The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design, to maximize the contribution and predictive value of the resulting data for clinical safety and therapeutic activity. We encourage sponsors to explore opportunities for reducing, refining, and replacing animal use in the preclinical program. For example, it may be appropriate to use *in vitro* or *in silico* testing to complement or replace animal studies. Sponsors are encouraged to submit proposals and justify any potential alternative approaches, which we will evaluate for equivalency to animal studies.

⁴ Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry, dated June 2015,
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf>

⁵ Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, dated May 1998,
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf>

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A. Natural History Studies

A thorough understanding of the natural history of a disease is an important element in all clinical development programs. Many degenerative retinal disorders are rare, and their natural history is often poorly characterized. Early in product development, sponsors should evaluate the depth and quality of existing natural history data. When such information is insufficient to guide clinical development, FDA recommends that a sponsor perform a careful natural history study to facilitate the product development program, although FDA does not require these studies. Early interactions between FDA and sponsors are welcome regarding the design of natural history studies (Ref. 4).

B. Study Design

To facilitate interpretation of clinical data, inclusion of a randomized, concurrent parallel control group is recommended for clinical trials whenever possible. Administration of the vehicle alone may serve as a control. In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit. When ethically acceptable, such a control is especially helpful early in clinical development, to evaluate bioactivity of the investigational GT product and possibly to provide initial evidence of its clinical efficacy. However, FDA acknowledges the risks associated with intravitreal and subretinal injection procedures and vehicles; without any prospect of direct benefit, these risks may not be acceptable under certain circumstances, such as for pediatric patients (21 CFR Part 50, Subpart D). Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought.

Measurement of certain efficacy and safety endpoints such as visual acuity is subjective, and results can be influenced by effort on the part of the patient, leading to a potential source of bias in the clinical trial. For trials intended to form the primary basis of an efficacy claim to support a marketing application, concurrent parallel group(s) should be used as a control (placebo or active) to decrease potential bias.

To further reduce potential bias, sponsors should include adequately-designed masking procedures. Differences between the procedure used for product delivery and a sham procedure may enable patients to distinguish the eye which received the product from that which received the sham treatment. FDA recommends at least two treatment arms, utilizing different doses but the same product administration procedures, to minimize patients' ability to identify their treatment arm, in addition to a sham control group. In addition to facilitating masking, the second treatment arm has value as a dose-ranging control.

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191 Although use of the contralateral eye to which the GT product is not administered as a
192 control may potentially be considered, it is generally not recommended due to the
193 following:

- 194
- 195 • For most indications in which GT products are likely to be used, the treated eye
196 and contralateral eye are often at different stages of disease at the time of trial
197 entry. In addition, disease progression in the two eyes is not necessarily similar
198 over the relatively short duration of the trial.
- 199
- 200 • When a patient is exposed to different procedures in the two eyes (e.g., one eye
201 receives a GT product and the other eye receives sham procedure), it frequently
202 leads to unmasking, which can confound the interpretation of the study results,
203 particularly for endpoints where patient effort can make a difference, such as
204 visual function measures.
- 205

206 C. Study Population

207

208 For clinical trials of GT products providing gene replacement, the correct genetic
209 diagnosis is essential for identifying potential participants. Thus, confirmation of the
210 genetic mutation prior to enrollment is recommended as an important element of the
211 clinical trial. If there are no readily available, reliable means of obtaining the needed
212 genetic diagnostic testing, a companion diagnostic may be needed and therefore should
213 be strongly considered early in development. If an *in vitro* companion diagnostic is
214 needed to appropriately select patients for study (and later, once the GT product is
215 approved, for treatment), then submission of the marketing application for the companion
216 diagnostic and submission of the biologics license application for the GT product should
217 be coordinated to support contemporaneous marketing authorizations.

218

219 Patients with severe visual impairment, or a disease that is likely to progress to severe
220 visual impairment, may be more willing to accept the potential or unknown risks of a
221 novel GT product, and those risks may be more readily justified in this population.
222 However, in some cases – for example, a GT product designed to restore function to
223 remaining viable retinal cells – severely affected patients may not benefit from
224 administration of the GT product nor would use in these patients provide information
225 about the effectiveness of the product. In general, first-in-human GT trials should enroll
226 patients with severities of visual impairment that offer a favorable benefit-risk profile. If
227 preliminary safety data supports further clinical development, sponsors may consider a
228 broader patient population in future trials.

229

230 Many retinal disorders affect both children and adults. For diseases that affect both
231 adults and children, trials in adult patients should be conducted prior to trials in pediatric
232 patients, whenever feasible. Since most rare diseases are pediatric diseases or have onset
233 of manifestations in childhood, pediatric studies are a critical part of drug development.
234 However, treatment in pediatric patients cannot proceed without addressing ethical
235 considerations for conducting investigations in vulnerable populations. Unless the risks

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236 of an investigational drug are no more than a minor increase over minimal risk (21 CFR
237 50.53), the administration of an investigational drug in children must offer a prospect of
238 direct clinical benefit to individually enrolled patients, the risk must be justified by the
239 anticipated benefit, and the anticipated risk-benefit profile must be at least as favorable as
240 that presented by accepted alternative treatments (21 CFR 50.52). Additionally, adequate
241 provisions must be made to obtain the permission of the parents and the assent of the
242 child as per 21 CFR 50.55.

243

D. Study Use

244

245
246 For early-phase trials, dose-ranging study designs are recommended. Comparing a range
247 of doses can identify potential therapeutic doses for a wider group of patients. The
248 choice of an initial dose and dose regimen should be supported by preclinical studies
249 and/or available clinical information. Such data should indicate that the initial dose is not
250 only reasonably safe, but also has therapeutic potential, particularly when the
251 administration procedure carries substantial risks.

252

253 Most retinal indications for which GT products are studied involve bilateral disease;
254 consideration, therefore, should be given during product development to the planned
255 administration of the GT product in both eyes. Because of safety concerns related to the
256 product, administration procedure, and any ancillary medications, administration to each
257 eye for an individual patient should be performed sequentially, rather than
258 simultaneously. While often the eye with more advanced disease receives the GT product
259 initially, a rationale should be developed for deciding which eye will receive the GT
260 product first. The time interval between administration in each eye should be carefully
261 planned for each patient based on preclinical data and available human experience. For
262 products intended for both eyes, the overall development plan prior to approval should
263 include clinical trials in which both eyes receive the GT product.

264

265 To ensure consistency across study sites, sponsors should include in the study protocol a
266 detailed description of the product delivery procedure and devices used for delivery.

267

268 A single administration of a GT product in each eye may not always be sufficient for a
269 variety of reasons. In such cases, careful studies, especially trials in humans, are
270 recommended to explore the feasibility of repeat administration in the same eye.

271

E. Safety Considerations

272

273
274 Intraocular administration (e.g., intravitreal or subretinal injection) may be the most
275 efficient method to deliver GT products intended for treatment of retinal disorders. Risks
276 of such procedures include intraocular infection, elevated intraocular pressure, media
277 opacities, and retinal damage. Therefore, the procedure should be performed by
278 individuals experienced in the method of planned delivery.

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280 Local or systemic immune responses to GT products may pose important safety risks.
281 For certain GT products, such as those using various viral vectors to introduce therapeutic
282 transgene(s) in vivo, immune reactions also may decrease transduction efficiency and
283 thereby diminish the treatment effect. Biomicroscopy and optical coherence tomography
284 are recommended to detect inflammatory reactions within the globe. To monitor
285 systemic immune reactions, immunoassays should be performed to measure cellular and
286 humoral immune responses to the vector and the transgene-encoded protein.

287
288 To minimize immune responses, immunosuppressants such as corticosteroids may be
289 considered before and after product administration. Immunosuppressant drugs may cause
290 increased intraocular pressure, cataracts, and other adverse events. Patients should be
291 closely monitored and treated as necessary to minimize the risk of developing glaucoma,
292 vision loss, and other complications.

293 294 **F. Study Endpoints**

295
296 Early-phase clinical trials typically focus on safety. However, for trials of GT products,
297 early assessment of potential clinical benefit is also important, particularly for rare
298 diseases with a limited number of patients available to participate in clinical
299 development. To guide further clinical development, FDA encourages sponsors to
300 explore a wide spectrum of potential clinical endpoints and other clinical effects in early-
301 phase trials. For example, sponsors may include endpoints based on retinal imaging
302 (optical coherence tomography, retinal photography, fluorescein angiography), visual
303 acuity (low and high luminance), visual fields, color vision, contrast sensitivity, other
304 measures of visual function (i.e., how well the eye and visual system function), and
305 functional vision (i.e., how well the patient performs vision-related activities of daily
306 living). For later-phase trials intended to provide substantial evidence of effectiveness to
307 support a marketing application, primary efficacy endpoints should reflect clinical
308 benefit, such as improvement in function or symptoms.

309
310 Examples of established efficacy endpoints that can be used to evaluate clinical benefit of
311 GT products intended for treatment of retinal disorders include:

- 312
- 313 • Best corrected distance visual acuity, measured with the Early Treatment of
314 Diabetic Retinopathy Study (ETDRS) chart or other visual acuity charts with an
315 equal number of letters per line and equivalent spacing between lines. A halving
316 (or doubling) of the visual angle represented by a gain (or loss), respectively, of at
317 least 15 letters on the ETDRS chart from baseline is considered clinically
318 meaningful.
 - 319 • Rate of photoreceptor loss, determined by measures such as optical coherence
320 tomography or autofluorescence photography. The comparison should be made
321 between the baseline and at least two subsequent area images, with intervals of 6
322 months or more between images. The best curve fit analyses demonstrating
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324 reduction in the rate of photoreceptor loss exceeding measurement uncertainty are
325 considered clinically meaningful.

326
327 FDA encourages sponsors to develop and propose novel endpoints to measure clinically
328 meaningful effects in patients with retinal disorders. This can be especially pertinent to
329 some rare retinal disorders for which the established efficacy endpoints may not be
330 appropriate to assess clinically meaningful effect of an investigational product. Sponsors
331 are welcome to engage FDA early in this process, and FDA is committed to working with
332 sponsors to develop acceptable endpoints.

333
334 • For example, a novel primary efficacy endpoint measuring mobility under
335 different levels of illumination was utilized to support marketing approval for
336 voretigene neparvovec-rzyl (a recombinant adeno-associated vector (AAV)
337 carrying the gene for human retinal pigment epithelium-specific 65 kDa protein).
338 During the clinical trials, the sponsor worked with FDA to develop this clinically
339 meaningful primary efficacy endpoint.

340 341 **G. Follow-Up Duration**

342
343 The length of follow-up to provide additional information regarding the safety and
344 efficacy of the GT product depends on many aspects of a GT product, including vector
345 persistence, genome integration, and transgene activity, and the goal of the follow-up
346 (e.g., safety vs. durability of clinical effect). In addition to monitoring for safety,
347 long-term follow-up is recommended to evaluate durability of the clinical effect. More
348 detailed discussion of long-term follow-up is provided in a separate FDA guidance
349 document (Ref. 3).

350 351 **H. Patient Experience**

352
353 Patient experience data⁶ may provide important additional information about the clinical
354 benefit of a GT product. FDA encourages sponsors to collect patient experience data
355 during product development, and to submit such data in the marketing application.

356
357

⁶ As defined in the section 569(c) of the Federal Food, Drug, and Cosmetic Act (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/developmentapprovalprocess/ucm579400.htm>

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358 **V. EXPEDITED PROGRAMS**

359
360 There are several programs that may be available to sponsors of GTs intended to address unmet
361 medical needs in the treatment of serious or life-threatening conditions that are intended to
362 facilitate and expedite development and review of these therapies, including regenerative
363 medicine advanced therapy designation, breakthrough therapy designation, fast track
364 designation, accelerated approval, and priority review. In particular, regenerative medicine
365 advanced therapy designation and breakthrough therapy designation call for earlier attention
366 from FDA to these potentially promising therapies, offering sponsors earlier and more frequent
367 interactions with FDA on efficient trial design and overall drug development. Further
368 information on these programs is available in separate guidance documents.^{7,8}

371 **VI. COMMUNICATION WITH FDA**

372
373 FDA recommends communication with OTAT early in product development, before submission
374 of an investigational new drug application (IND.) There are different meeting types that can be
375 used for such discussions, depending on the stage of product development and the issues to be
376 considered. These include pre-IND meetings and, earlier in development, INitial Targeted
377 Engagement for Regulatory Advice on CBER productTs (INTERACT) meetings.⁹ Early
378 nonbinding, regulatory advice can be obtained from OTAT through an INTERACT meeting,
379 which can be used to discuss issues such as a product's early preclinical program, and/or through
380 a pre-IND meeting prior to submission of the IND (Ref. 5).

381

⁷ Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, dated May 2014,
<https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf>

⁸ Expedited Programs for Regenerative Medicine Therapies for Serious Conditions: Draft Guidance for Industry,
dated November 2017, (when finalized),
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf>

⁹ Going forward, INTERACT meetings will serve in place of pre-pre-IND meetings. For additional information
about INTERACT meetings, please see
<https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm>.

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

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