

Long Term Follow-Up After Administration of Human Gene Therapy Products

Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018

Contains Nonbinding Recommendations

Draft – Not for Implementation

Table of Contents

I.	INTRODUCTION.....	1
II.	SCOPE	2
III.	BACKGROUND	2
	A. Potential Risks of Delayed Adverse Events Following Exposure to Human Gene Therapy Products.....	2
	B. History.....	3
	C. Experience Gained Through Long Term Follow-up of Subjects in Gene Therapy Trials.....	4
	D. Long Term Follow-up for Novel Gene Therapy Products	5
IV.	PRECLINICAL DATA USED FOR ASSESSMENT OF DELAYED RISKS IN GENE THERAPY CLINICAL TRIALS.....	5
	A. Criteria to Assess Potential Delayed Risks of Gene Therapy Products.....	5
	B. Considerations for Preclinical Study Design to Assess Biodistribution and Persistence of Gene Therapy Product.....	9
	C. Vector Persistence, Integration, Reactivation and Genome Modification: Assessing Long Term Risks.....	11
	D. Considerations for Preclinical Evaluation of Products that Involve Genome Editing.....	15
V.	RECOMMENDATIONS FOR PROTOCOLS FOR LONG TERM FOLLOW-UP OBSERVATIONS: CLINICAL CONSIDERATIONS.....	15
	A. Goals of the Long Term Follow-up Observations.....	15
	B. Clinical Trial Populations for Long Term Follow-up Observations.....	16
	C. Duration of Long Term Follow-up Observations	16
	D. Elements of Long Term Follow-up Observations	17
	E. Informed Consent in Trials Involving Long Term Follow-up Observations	21
	F. Special Considerations Regarding Integrating Vectors	22
	G. Special Considerations Regarding Product Involving Genome Editing.....	26
VI.	GENERAL CONSIDERATIONS FOR POST-MARKETING MONITORING PLANS FOR GENE THERAPY PRODUCTS	26
VII.	LONG TERM FOLLOW-UP UNDER SPECIAL CIRCUMSTANCES	27
VIII.	DEFINITIONS	28
IX.	REFERENCES.....	30
	APPENDICES.....	32

Contains Nonbinding Recommendations

Draft – Not for Implementation

**Long Term Follow-Up After Administration of Human Gene
Therapy Products**

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are providing you, a sponsor who is developing a human gene therapy (GT) product,¹ recommendations regarding the design of long term follow-up observational studies (LTFU observations) for the collection of data on delayed adverse events following administration of a GT product. Often, GT products are designed to achieve therapeutic effect through permanent or long-acting changes in the human body. As a result of long term exposure to an investigational GT product, study subjects may be at increased risk of undesirable and unpredictable outcomes which may present as delayed adverse event(s). To understand and mitigate the risk of a delayed adverse event, subjects in gene therapy trials may be monitored for an extended period of time, which is commonly referred to as the “long term follow-up” (LTFU) period (of a clinical study). LTFU observations are extended assessments that continue some of the scheduled observations of a clinical trial past the active follow-up period, and are an integral portion of the study of some investigational GT products. LTFU observations are important to monitor long term safety of GT products. For GT products that present long term risks to subjects, LTFU/surveillance plan(s) should also be put in place post-licensure for monitoring of delayed adverse events (for details we refer you to section VI. of this document). Not all GT products will require LTFU observations; a risk assessment is performed by a sponsor based on several factors as outlined in this guidance.

In this guidance, we provide a brief introduction of the product characteristics, patient-related factors, and the preclinical and clinical data that should be considered when assessing the need for LTFU observations for your GT product. We also provide recommendations for the study design of LTFU observations with specific considerations for different gene therapy products and recommendations on patient monitoring for licensed GT products. Definitions of terms used throughout this guidance are provided in section VIII. of this document.

¹ See section VIII. Definitions: Human gene therapy product.

Contains Nonbinding Recommendations

Draft – Not for Implementation

42 This draft guidance, when finalized, is intended to supersede the document entitled “Guidance
43 for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events”
44 dated November 2006 (Ref. 1) (2006 Delayed Adverse Events). This draft guidance, when
45 finalized, is also intended to supplement the guidance entitled “Testing of Retroviral Vector-
46 Based Human Gene Therapy Products for Replication Competent Retrovirus during Product
47 Manufacture and Patient Follow-up; Draft Guidance for Industry” dated July 2018.

48
49 FDA’s guidance documents, including this draft guidance, do not establish legally enforceable
50 responsibilities. Instead, guidances describe the FDA’s current thinking on a topic and should be
51 viewed only as recommendations, unless specific regulatory or statutory requirements are cited.
52 The use of the word *should* in FDA’s guidances means that something is suggested or
53 recommended, but not required.

54 55 56 **II. SCOPE**

57
58 This guidance applies to all GT clinical studies and to licensed GT products for which LTFU
59 observations are warranted based on analyses of available preclinical and clinical safety data for
60 the GT product that raises concerns for delayed adverse events. The recommendations in this
61 guidance apply to gene therapies that produce long lasting genetic effects (that is, gene therapy
62 that represents more than just transient expression of a gene) and the performance of LTFU
63 observations for evidence of delayed adverse events, i.e., adverse events that occur past the
64 active follow-up period after exposure to the GT product, as described in the main study
65 protocol.

66 67 68 **III. BACKGROUND**

69 70 **A. Potential Risks of Delayed Adverse Events Following Exposure to Human** 71 **Gene Therapy Products**

72
73 Characteristics unique to human GT products that may be associated with delayed
74 adverse events include:

- 75
76 1. The integration activity of the GT product: The biological activity of
77 retroviral vectors² (e.g., vectors derived from gammaretrovirus, lentivirus,
78 foamy virus etc.) and transposon elements is imparted by an integration
79 event in the genome. In general, such integration is not directed to
80 specific sites in the human genome, and this raises the potential for
81 disruption of critical host (human) genes at the site of integration, or
82 activation of proto-oncogenes near the integration site(s) and, thereby, the
83 risk for malignancies.

84

² See section VIII. Definitions: Vector.

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
2. Genome editing activity: Genome editing based GT products impart their biological activity through site-specific changes in the human genome, but may also have off-target effects on the genome (Ref. 2). Similar to integrating vectors, genome editing may produce undesirable changes in the genome (whether *ex vivo* or *in vivo*), with the risk of malignancies, impairment of gene function, etc.
 3. Prolonged expression: A GT product where the transgene (therapeutic gene) encodes growth factors, such as vascular endothelial growth factor (VEGF) or proteins associated with cell division such as p53, may raise the potential for unregulated cell growth and malignancies due to prolonged exposure to the therapeutic protein. Similarly, transgenes encoding immune recognition factors, such as chimeric antigen receptors or T-cell receptors, introduce the risk for autoimmune-like reactions (to self-antigens) upon prolonged exposure. For GT products that carry transcriptional regulatory elements (e.g., microRNA) or immune-modulatory proteins (e.g., cytokines) there is also the risk of unknown pleotropic effects, including altered expression of host (human) genes that could result in unpredictable and undesirable outcomes.
 4. Latency: When the GT product has the potential for latency, such as a herpesvirus, there is the potential for reactivation from latency and the risk of delayed adverse events related to a symptomatic infection.
 5. Establishment of persistent infections: GT products that are replication competent viruses and bacteria, such as listeria-based bacterial vectors, have the potential to establish persistent infections in immunocompromised patients leading to the risk of developing a delayed but serious infection.

115 In addition to product-related factors, the long term risk profile of a GT product should
116 also take into consideration the target cell/tissues/organ, and the patient population (age,
117 immune status, risk of mortality etc.), and the relevant disease characteristics.

118 **B. History**

119
120
121 The recommendations for LTFU monitoring in the 2006 Delayed Adverse Events
122 guidance (Ref. 1) were based on extensive discussions among gene therapy stakeholders,
123 and cumulative preclinical and clinical experience with GT products (Refs. 3, 4, 5) as
124 summarized in this section. To discuss and solicit advice about long term risks to
125 subjects exposed to such products, three separate meetings of the FDA advisory
126 committee, Biological Response Modifiers Advisory Committee (BRMAC), were
127 convened on November 17, 2000, April 6, 2001, and October 24, 2001 (Ref. 6).
128

Contains Nonbinding Recommendations

Draft – Not for Implementation

129 A public workshop entitled “Long-term Follow-Up of Participants in Human Gene
130 Transfer Research” was also held in June 2001, in association with the annual meeting of
131 the American Society of Gene Therapy (ASGT). The workshop included a forum in
132 which invited speakers discussed the challenges associated with LTFU of subjects in
133 gene therapy clinical studies. The workshop organizers published a summary of the
134 discussion (Ref. 7).

135
136 Taking these discussions into consideration, we provided detailed recommendations in
137 the 2006 Delayed Adverse Events guidance document on the duration and design of
138 LTFU observations (Ref. 1). The Agency advised sponsors to observe subjects for
139 delayed adverse events for as long as 15 years following exposure to the investigational
140 GT product, specifying that the LTFU observation was to include a minimum of five
141 years of annual examinations, followed by ten years of annual queries of study subjects,
142 either in person or by questionnaire.

143
144 Herein, we update our recommendations in the guidance taking into account the clinical
145 experience gained since 2006 in LTFU of investigational GT products (as described in
146 the following section), and the development of novel GT products with emerging
147 technologies such as genome-editing that may be associated with an increased risk of
148 delayed adverse events (as described in section III.D of this document).

149 **C. Experience Gained Through Long Term Follow-up of Subjects in Gene** 150 **Therapy Trials**

151
152 To date, leukemias have been reported in more than one trial where subjects have
153 received genetically-modified cells that were manufactured using gammaretroviral
154 vectors (Refs. 8-11). Advances in analytical approaches for integration site analysis in
155 patient samples collected during LTFU have provided insight into the possible
156 mechanisms involved in the occurrence of such delayed adverse events (Refs. 8-14).

157
158 Past clinical experience in LTFU monitoring, and significant improvements in analytical
159 approaches to investigate the integration site have contributed greatly towards our
160 understanding of the risks associated with integrating gene therapy vectors (Ref. 15).
161 Such risks can be mitigated through improvements in vector design and the duration and
162 design of LTFU observations. Because integrating gene therapy vectors can persist in the
163 body over the life-span of the patient’s transduced cells, vectors with an improved risk
164 profile were desired, and have subsequently been developed for clinical use (Refs. 16,
165 17). These include gammaretroviral and lentiviral vectors modified:

- 166
167
168 1. To reduce the risk of activating host genes adjacent to the integration site
169 (e.g., self-inactivating (SIN) vectors and vectors containing insulator
170 sequences);
- 171
172 2. To be less genotoxic (e.g., carrying non-viral physiological promoters to
173 drive the expression of the therapeutic gene); and

Contains Nonbinding Recommendations

Draft – Not for Implementation

174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217

3. To reduce the potential for recombination, and thereby, the risk of generating replication competent, pathogenic variants.

D. Long Term Follow-up for Novel Gene Therapy Products

Novel GT products developed as a result of emerging technologies, such as transposon-based gene insertion and genome editing, also raise concerns for delayed adverse events due to the unique genome modifying activity of such products. Specifically, a vector with a transposon element can insert transgenes into the host chromosome randomly by a direct “cut-and-paste” mechanism, mediated by the transposases (enzyme) activity in the product (Ref. 18). A GT product with genome editing components (nucleases) can give rise to non-specific off-target changes in the genome (Ref. 2), and may be associated with unknown and unpredictable risks for developing delayed adverse events in study subjects and patients once approved. The LTFU observations for these novel GT products should be designed to take into account product-specific characteristics, the basic and translational knowledge generated in the field, and the product-specific preclinical data generated to enable investigational new drug application (IND) studies, as described in the following section.

IV. PRECLINICAL DATA USED FOR ASSESSMENT OF DELAYED RISKS IN GENE THERAPY CLINICAL TRIALS

A. Criteria to Assess Potential Delayed Risks of Gene Therapy Products

To assess the risk of delayed adverse events for a GT product, we recommend that you use available preclinical and clinical evidence, and current information about your product and similar products based on studies that you and others have performed. In general, when the risk of delayed adverse events is low following exposure to a GT product, LTFU observations are not recommended. We consider the assessment of risk to be a continuous process; in that, as more data accumulates, we recommend that you reassess the risk to your subjects and, if appropriate, revise an existing LTFU observations or initiate a LTFU observation, if previously allowed to proceed without LTFU observations.

Pertinent previous preclinical and clinical experience with your product or similar products is highly relevant in the assessment of the risk for delayed adverse events. For example, experience with GT products in the same vector class, administered by a similar route, or given for the same clinical indication may contribute helpful information. However, for novel products such information may not be available or pertinent, or may be limited, in which case data from well-designed preclinical studies (as described in section IV.B of this document) should be used in assessing the risk of delayed adverse

Contains Nonbinding Recommendations

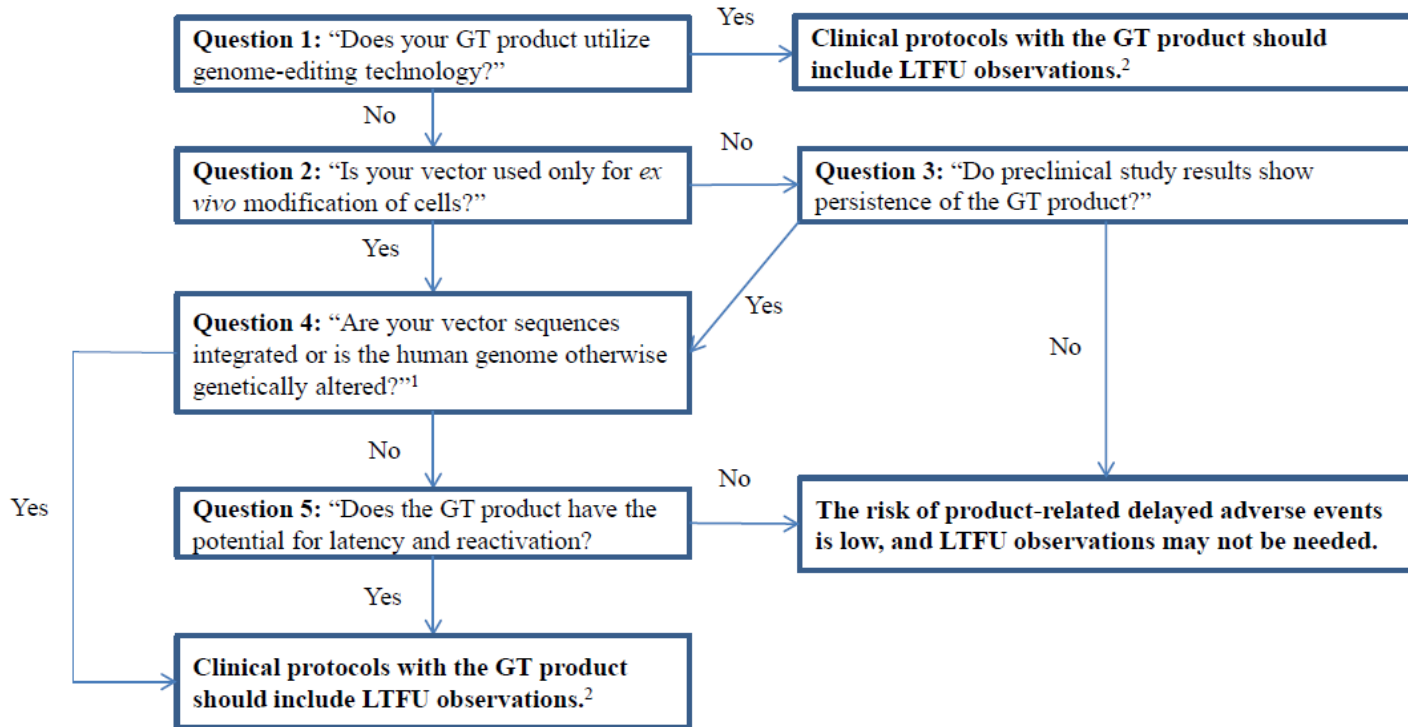
Draft – Not for Implementation

218 events. Primary data and information relevant to the assessment of the risk of delayed
219 events should be submitted in your IND along with other preclinical data (see 21 CFR
220 312.23(a)(8), 312.23(a)(10)(iv), and 312.42(a)(11)).

221
222 GT product knowledge is critical in assessing the level of risk for delayed adverse events
223 and the need for LTFU observations. To help you in this process, we refer you to section
224 III.A of this document, and to the series of questions in Figure 1, “Framework to Assess
225 the Risk of Gene Therapy-Related Delayed Adverse Events.”

226
227

Figure 1. Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events



228
229
230 ¹ If you have evidence that suggests that the product may integrate or if the product was intentionally
231 designed to facilitate integration (please refer to Table 1, section IV.C of this document); the answer is
232 “yes.”

233 ² See section V. of the text for recommendations on how to perform clinical LTFU observations.

234 Note, that evidence from preclinical studies will help you answer questions 3 through 5
235 below and in Figure 1. When the risk of delayed adverse events is low based on your
236 answers to these questions, a plan for LTFU observations may not be necessary to
237 mitigate risks to subjects.

238
239 We suggest you use the framework in Figure 1 by answering the questions in sequence as
240 follows:

241
242

Contains Nonbinding Recommendations

Draft – Not for Implementation

243 **Question 1:** “Does your GT product utilize genome-editing technology?”
244

245 If the answer is “no,” go to Question 2. If the answer is “yes,” all your clinical
246 protocols proposing administration of the GT product should include LTFU
247 observations for appropriate human subject protections (see section V. for
248 recommendations on how to perform clinical LTFU observations).
249

250 **Question 2:** “Is your vector used only for *ex vivo* modification of cells?”
251

252 If the answer is “no,” go to Question 3. If the answer is “yes,” go to Question 4.
253

254 **Question 3:** “Do preclinical study results show persistence of the GT product?”
255

256 If the answer is “no,” the risk of product-related delayed adverse events is low,
257 and LTFU observations may not be needed. If the answer is “yes,” go to
258 Question 4.
259

260 If it is unknown whether your GT product persists, for the purpose of assessing
261 the risk of delayed adverse events, we recommend that you either assume that the
262 GT product does persist, or perform preclinical studies to assay for the GT
263 product persistence in a relevant animal species. For the design and details of
264 such preclinical studies, please refer to section IV.B of this document;
265 specifically, the polymerase chain reaction (PCR) assay for determining vector
266 persistence in biodistribution studies. Following administration of the product,
267 persistence is indicated by detectable levels of GT product sequences above the
268 threshold level of the PCR assay, and absence of an apparent downward trend
269 over several time points. In contrast, persistence is unlikely if product sequences
270 cannot be detected with a sensitive assay such as PCR or if the assay for GT
271 product sequences demonstrates a downward trend over time. We encourage you
272 to consult with the Office of Tissues and Advanced Therapies (OTAT) at the
273 Center for Biologics Evaluation and Research (CBER) for specific advice
274 regarding determination of GT product persistence and biodistribution in your test
275 system.
276

277 **Question 4:** “Are your vector sequences integrated or is the human genome
278 otherwise genetically altered?”
279

280 If the answer is “no,” go to Question 5. If you have evidence that suggests that
281 the product may integrate or if the product was intentionally designed to facilitate
282 integration (please refer to Table 1, section IV.C of this document); the answer is
283 “yes.” If the answer is “yes,” all your clinical protocols proposing administration
284 of the GT product should include LTFU observations for appropriate human
285 subject protections (see section V. for recommendations on how to perform
286 clinical LTFU observations).
287

Contains Nonbinding Recommendations

Draft – Not for Implementation

288 **Question 5:** “Does the GT product have the potential for latency and
289 reactivation?”

290
291 If the answer is “no,” the risk of product-related delayed adverse events is low,
292 and LTFU observations may not be needed. If the answer is “yes,” all your
293 clinical protocols with the GT product should include LTFU observations for
294 appropriate human subject protections (see section V. for recommendations on
295 how to perform clinical LTFU observations).
296

297 Laboratory and preclinical evidence of a low risk of delayed adverse events following
298 exposure to a similar GT product may show that LTFU observations for your GT product
299 are not needed. When such data/information is made available for review, we can assess
300 their relevance to your product if you provide adequate details and a clear explanation of
301 similarities and differences between the two products. For additional guidance, we
302 provide the following two examples:
303

- 304 • Your GT product is a plasmid, and the similar product is also a plasmid,
305 but has different coding sequences for the proposed therapeutic gene
306 product. The similar product has been used in preclinical and clinical
307 studies, administered by an identical route and in an identical final
308 formulation to that proposed in the prospective studies in your program. In
309 this case, reference to a published study demonstrating lack of persistence
310 of the vector sequence for the similar (plasmid) product may adequately
311 address concerns regarding the persistence of the proposed vector (your
312 plasmid).
313
- 314 • Your GT product and the similar product differ only with respect to route
315 of administration. The similar product was administered into tumors
316 (intratumorally). Your GT product is to be administered intravenously.
317 There is a published study demonstrating the lack of persistence of the
318 similar product when administered intratumorally. In this case, the data is
319 not sufficiently relevant to the GT product under study, since there was no
320 intended systemic exposure to the product. Thus, there is insufficient
321 similarity to conclude that LTFU observations are not necessary in your
322 proposed study to mitigate the long term risks to subjects. In the absence
323 of relevant data from a study involving a similar product, we recommend
324 that you assess the risk of product persistence in a preclinical study with
325 the proposed GT product administered by the intravenous route.
326

327 If you believe you have evidence from studies on a similar product that is adequate to
328 support conclusions that either the GT product is unlikely to persist in human hosts, or
329 the vector sequence does not integrate into the human genome and the GT product does
330 not have the potential for latency and reactivation, you may decide to submit a clinical
331 protocol that does not provide for LTFU observations. We will review such submissions
332 and, if based upon our review of your submission or other additional information, we

Contains Nonbinding Recommendations

Draft – Not for Implementation

333 conclude that LTFU observations for delayed adverse events are necessary to mitigate
334 long term risks, and that without LTFU observations, the study presents an unreasonable
335 and significant risk to study subjects, we may place your study on clinical hold (21 CFR
336 312.42(b)(1)(i) and 312.42(b)(2)(i)).

337
338 We provide the following examples of evidence obtained from investigation of a product
339 that may warrant our recommendation of LTFU observations for delayed adverse events:

- 340
341 • A preclinical toxicology study indicates that expression of the therapeutic
342 gene (the transgene in your product) is associated with delayed toxicity.
- 343
344 • The therapeutic gene provides functional replacement of a host gene that
345 is otherwise not expressed, and the therapeutic protein is potentially
346 immunogenic.
- 347
348 • Data collected in a clinical study with your GT product indicates product
349 persistence, even though data from your preclinical studies suggested that
350 the product did not persist.
- 351
352 • Data collected in a clinical study with your GT product identifies an
353 increased risk of delayed adverse events.

354 **B. Considerations for Preclinical Study Design to Assess Biodistribution and** 355 **Persistence of Gene Therapy Product**

356
357
358 As discussed in section III.A of this document, product persistence heightens the risk of
359 delayed adverse events following exposure to the GT product. Indeed, the longer the GT
360 product persists, the greater the duration and degree of risk of delayed adverse events.
361 We recommend that you perform preclinical biodistribution studies using methods shown
362 to be sensitive and quantitative to detect product sequences. Such studies would be
363 designed to determine the distribution of your product in non-target tissues and the
364 persistence of the product in both non-target and target tissues following direct *in vivo*
365 administration of the product. If possible and applicable, we recommend that the studies
366 employ an animal species that permits vector transduction and/or vector replication and
367 that the animal species be biologically responsive to the specific transgene of interest or
368 to therapeutic components in the product (e.g., for products that may not contain
369 transgenes and only genome editing components) (Ref. 19). The duration of the
370 preclinical studies will vary, depending on the animal model employed. Projections of
371 delayed adverse reactions in human subjects may be derived from assessment of data
372 from appropriate long term observational studies in animals, when such observational
373 studies are possible.

374
375 A biodistribution study in animals can be performed either as a separate study or as a
376 component of a toxicology study. Consider the following points in your animal study
377 design to permit evaluation of GT product localization and persistence (Ref. 20).

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
1. Animal Study Design
 - a. Use the GT product in the final formulation proposed for the clinical study because changes in the final formulation may alter biodistribution pattern.
 - b. Use both genders or justify the use of a single gender.
 - c. Use at least 5 animals per gender per group per sacrifice time point for rodents, and between 3-5 animals per gender per group per sacrifice time point for non-rodents.
 - d. Consider factors in the study design that might influence or compromise the GT product distribution and/or persistence such as the animal's age and physiologic condition.
 - e. Use the intended clinical route of GT product administration, if possible.
 - f. Assess GT product biodistribution in a vehicle control group and a group of animals that receives the maximum feasible dose (MFD) or clinically relevant dose (defined in section VIII). Studies at additional dose levels might provide information on dose-dependent effects of your product.
 - g. Include appropriate safety endpoints in your biodistribution study to assess any potential correlation between product presence/persistence and adverse findings if safety endpoints have not been evaluated already in a separate toxicology study using the same animal model. These safety endpoints should include clinical observations, body weights, clinical pathology, gross organ pathology, and histopathology.
 - h. Include several sacrifice intervals to characterize the kinetics of GT product distribution and persistence. We recommend sacrifice of animals at the expected time of peak GT product detection and at several later time points to evaluate clearance of product sequences from tissues.
 2. Tissue Collection and Analysis
 - a. Sample and analyze the following panel of tissues, at a minimum: blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen. Consider other tissues for evaluation, depending on the product, vector type and tropism, and transgene(s), as well as the route of administration (e.g., draining lymph nodes and contralateral sites for subcutaneous/intramuscular injection, bone marrow, eyes, etc.).
 - b. Choose a method for tissue collection that avoids the potential for cross contamination among different tissue samples.

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 422 c. Use a quantitative, sensitive assay like PCR assay to analyze the
423 samples for vector sequences. You should submit data to your
424 IND to demonstrate that your assay methodology is capable of
425 specifically detecting vector sequence in both animal and human
426 tissues. We recognize that analytical technologies are constantly
427 changing, and encourage you to discuss the assay methodology
428 with us before initiating sample analysis. Our current PCR
429 recommendations include the following:
430
- 431 i. The assay should have a demonstrated limit of quantitation
432 of ≤ 50 copies of product per 1 μg genomic DNA, so that
433 your assay can detect this limit with 95% confidence.
 - 434 ii. You should use a minimum of three samples per tissue.
435 One sample of each tissue should include a spike of control
436 DNA, including a known amount of the vector sequences,
437 to assess the adequacy of the PCR assay reaction. The
438 spike control will determine the specified PCR assay
439 sensitivity.
 - 440 iii. You should provide a rationale for the number of replicates
441 for testing per tissue, taking into account the size of the
442 sample relative to the tissue you are testing.
- 443
- 444 3. Other Considerations
- 445
- 446 There are many variables that will affect the outcome and interpretation of
447 the *in vivo* assessment of each GT product type. Hence, we encourage you
448 to discuss with OTAT the study design for your GT product before
449 initiating the preclinical biodistribution study to ensure that both
450 biodistribution and persistence will be adequately assessed³.

C. Vector Persistence, Integration, Reactivation and Genome Modification: Assessing Long Term Risks

455 GT products may or may not use technologies that modify the host genome. For products
456 that do, such as integrating vectors (gammaretrovirus, lentivirus, foamy virus etc.),
457 herpesvirus capable of latency-reactivation, and genome editing products (as described
458 under sections III.A and III.D of this document, respectively), there is the risk of delayed
459

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 replace animal studies. Sponsors are encouraged to submit proposals and justify any potential alternative approaches, which we will evaluate for equivalency to animal studies.

Contains Nonbinding Recommendations

Draft – Not for Implementation

460 adverse events. Accordingly, as depicted in Table 1 of this document and in the answer
461 to Question 4 in Figure 1, it is important to conduct LTFU observations to mitigate
462 delayed risks to subjects receiving GT products with integrating activity.
463

464 We are aware that the potential of vectors to integrate may be modified to increase their
465 utility as gene therapy agents; for example, a vector can be modified to induce integration
466 of its DNA (Refs. 21-24). Another example would be changes in the methods used to
467 introduce plasmid DNA vectors into cells that result in higher integration frequencies
468 (Ref. 25). In those cases where a modification of the GT product may have altered its
469 persistence or integration properties, we recommend that you submit data to your IND
470 from preclinical studies to assess vector persistence in an appropriate model and take one
471 of the following actions:

- 472
473 1. If the vector is not persistent, the predicted risk of delayed adverse events
474 would appear to be low in which case LTFU observations may not be
475 needed.
476
- 477 2. If the vector is persistent, we recommend that you perform preclinical
478 studies to assess vector integration, as well as the potential for vector
479 latency and reactivation.
480
- 481 3. If the studies show no evidence for persistence due to integration of the
482 genetic material or development of latency, the predicted risk of delayed
483 adverse events would be low. LTFU observations may not be needed.
484
- 485 4. If the studies show no evidence for integration of the genetic material but
486 studies for latency and reactivation are inconclusive, cannot be performed,
487 or show evidence of latency and/or reactivation, the predicted risk of
488 delayed adverse events is indeterminate. LTFU observations may be
489 recommended for human subject protections.
490
- 491 5. If preclinical studies of vector integration are not feasible, if the
492 therapeutic gene/genetic material integrates, or if the vector is shown to
493 persist in a latent state that may be reactivated, the risk of delayed adverse
494 events is high or unknown, and LTFU observations in study subjects are
495 recommended for human subject protection.
496
- 497 6. If vector integration studies are not performed, we recommend that you
498 provide other evidence to support an assessment that your product does
499 not pose high risks of delayed adverse events, including the following:
500
 - 501 a. A discussion of why vector integration studies were not performed.
 - 502 b. The evidence supporting your assessment of the risk of delayed
503 adverse events posed by your product.
504

Contains Nonbinding Recommendations

Draft – Not for Implementation

505 As stated in section IV.B.3 of this document, we encourage you to discuss with FDA
506 your study design before starting the trial.

507
508 GT products that are based on vectors such as plasmids, poxvirus, adenovirus, and adeno-
509 associated virus vectors (AAV) that do not have a propensity to integrate or reactivate
510 following latency, generally present a lower risk of delayed adverse events. Clinical data
511 from LTFU observations of subjects that have received plasmids, poxvirus, adenovirus,
512 and AAV in trials conducted since 2006, further supports the assessment of lower risk for
513 these GT products. However, vector or product-specific modifications may alter the risk
514 profile of products that are currently considered lower risk, for example a plasmid that is
515 modified to carry genome editing components. Conversely, gene therapy vectors
516 currently considered to pose delayed risks might be modified in order to reduce those
517 risks. Hence, data supporting decreased or increased risk for delayed adverse events with
518 novel GT products or vector types could provide the basis for sponsors to reassess our
519 recommendations for performing LTFU observations. We encourage you to consult with
520 OTAT regarding a reassessment of our recommendations for performing LTFU
521 observations.
522

Contains Nonbinding Recommendations

Draft – Not for Implementation

523 **Table 1. Propensity of Commonly Used Gene Therapy Products/Vectors to Modify the**
 524 **Host Genome**
 525

Product/Vector Type	Propensity to Modify Genome¹	Long Term Follow-up Observations²
Plasmid	No	No
RNA	No	No
Poxvirus	No	No
Adenovirus	No	No
Adeno-associated virus ³	No	Product specific (2-5 years)
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes
Transposon elements	Yes	Product specific
Microbial vectors for gene therapy (MVGT) ⁴	No, but may persist and undergo reactivation	Product specific
Genome editing products	Yes; permanent changes to the host genome	Yes

526 ¹ Based on product design (i.e., lack of any known mechanism to facilitate integration or genome editing), as well as
 527 cumulative preclinical and clinical evidence suggesting that a GT product does not integrate into or edit the genome
 528 or integrates in/modifies the genome at very low frequencies.

529 ² Specific circumstances that indicate persistent expression of the transgene, in the absence of integration or genome
 530 editing, may be the basis for a conclusion that LTFU observations are recommended to mitigate long term risks to
 531 subjects receiving these vectors. This would depend on additional criteria, such as the transgene expressed or
 532 clinical indication, as described in this section.

533 ³ Replication-negative vectors only.

534 ⁴ For additional guidance we refer you to “Recommendations for Microbial Vectors used for Gene Therapy;
 535 Guidance for Industry” dated September 2016,

536 <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>.

538

Contains Nonbinding Recommendations

Draft – Not for Implementation

539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581

D. Considerations for Preclinical Evaluation of Products that Involve Genome Editing

Genome editing, whether *ex vivo* or *in vivo*, introduces the risk for delayed adverse effects, due to 1) the permanent nature of change; 2) the potential for off-target genome modifications that can lead to aberrant gene expression, chromosomal translocation, induce malignancies, etc.; 3) the risk for insertional mutagenesis when integrating vectors are used to deliver the genome editing components, and the associated risk of tumorigenicity; and/or 4) the possibility of an immune response to the genome-editing components or the expressed transgene. Preclinical safety evaluation of genome editing products should consider: 1) the technology used to edit the genome; 2) the cell type that is modified *ex vivo*; 3) the vector used to deliver the genome-editing components; and 4) the clinical route of administration. Preclinical studies evaluating these factors can inform the scope of the clinical LTFU observations.

For guidance on the biodistribution studies when considering the vector type in the genome edited product, and the related long term risks with integrating vectors, we refer you to sections IV.B and IV.C of this document.

V. RECOMMENDATIONS FOR PROTOCOLS FOR LONG TERM FOLLOW-UP OBSERVATIONS: CLINICAL CONSIDERATIONS

In this section, we recommend elements appropriate to the design and conduct of LTFU observations for delayed adverse events in study subjects receiving investigational GT products. Typically, LTFU observations are conducted under a protocol (LTFU protocol) that is separate from the main study protocol, and may begin immediately after the main study protocol ends.

A. Goals of the Long Term Follow-up Observations

The objective of LTFU observations in clinical development of a GT product is to identify and mitigate the long term risks to the patients receiving the GT product. The LTFU protocol for GT trials is primarily designed to capture delayed adverse events in study subjects as well as to understand the persistence of the GT product. As a sponsor, you may consider designing the LTFU protocol to assess the long term clinical efficacy, and durability of your product. For additional guidance on trial design for GT products we refer you to FDA’s guidance document “Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry” dated August 2015 (Ref. 26). Please refer to Appendix 1 of this document for a LTFU Annual Report Template.

Contains Nonbinding Recommendations

Draft – Not for Implementation

582 **B. Clinical Trial Populations for Long Term Follow-up Observations**

583
584 When a GT product is deemed to pose a risk for delayed adverse events (based on the
585 recommendations/discussions provided under sections III and IV of this document) and a
586 decision to perform LTFU observations is made, all study subjects who receive the GT
587 product are expected to be enrolled in the LTFU protocol after signing an informed
588 consent document. LTFU observations may have reduced utility in assessing and
589 mitigating subject risk when the population selected for the trial has characteristics that
590 could confound the observation of the delayed adverse events, such as short life
591 expectancy, multiple co-morbidities, and exposure to other agents such as radiation or
592 chemotherapy. In contrast, LTFU observations could have greater value in assessing and
593 mitigating the risks to subjects who have limited disease or are disease-free, and who
594 have few co-morbidities and limited exposures to other agents with potential for delayed
595 adverse events. Hence, characteristics of the patient population and the disease to be
596 treated should be considered when designing a LTFU protocol.

597 **C. Duration of Long Term Follow-up Observations**

598
599 It is important that the design of LTFU observations be appropriate to detect potential
600 gene therapy-related delayed adverse events in the study subjects enrolled in your clinical
601 studies. The duration of LTFU should be sufficient to observe the subjects for risks that
602 may be due to the characteristics of the product, the nature of the exposure, and the
603 anticipated time of occurrence of delayed adverse events. Elements that will influence
604 the determination of the duration of LTFU observations include the following:
605
606

- 607 • The observed duration of *in vivo* product persistence.
- 608 • The observed duration of transgene expression.
- 609 • Product characteristics *in vivo*.
- 610 • Route of administration.
- 611 • The expected survival rates and the known background rates of the events
612 of interest occurring in the study population.
- 613 • Other factors that may be relevant to the feasibility and scientific value of
614 conducting LTFU observations; for example, the durability of the clinical
615 effect.

616
617 In general, our current recommendations for the duration of a LTFU protocol based on
618 product type are as follows:
619

- 620 • Fifteen years for integrating vectors such as gammaretroviral and lentiviral
621 vectors and transposon elements.
 - 622 • Up to fifteen years for genome editing products.
 - 623 • Up to five years for AAV vectors.
- 624

Contains Nonbinding Recommendations

Draft – Not for Implementation

625 Additionally, a risk-based approach for determining the duration of a LTFU protocol may
626 be considered for vectors capable of latency (e.g., Herpesvirus) or long term expression
627 without integration (e.g., AAV).
628

629 Although these recommendations are broadly based on GT product type, you should also
630 consider the elements listed above, in this section, as it applies to your GT product,
631 disease characteristics, and the patient population, in addition to the discussions in
632 sections III. and IV. of this document.
633

634 To reduce the unnecessary burden to study subjects and to you as the study sponsor, it
635 may be appropriate to modify the duration of the LTFU observation based on your
636 ongoing assessment of product persistence, transgene expression, and clinical findings. If
637 you intend to modify the duration of the follow-up, you may submit an amendment to
638 your IND justifying the change to your LTFU protocol, and communicate with FDA to
639 reach a final decision (we refer you to section V. of this document for additional guidance
640 regarding amendments to the clinical protocol).
641

D. Elements of Long Term Follow-up Observations

642
643

644 We recommend that at least the following general elements be part of the LTFU protocol:
645

- 646 • You should establish a dedicated clinical LTFU protocol detailing patient
647 visit schedules, sampling plan (for patient test samples, such as blood),
648 methods of monitoring tests, and clinical events of interest that will be
649 monitored over the entire LTFU observation.
650
- 651 • The investigator is required to prepare and maintain adequate and accurate
652 case histories that record all observations and other data pertinent to the
653 investigation on each subject administered the investigational drug or
654 employed as a control in the investigation (see 21 CFR 312.62(b)). These
655 records would include a baseline history prior to exposure to the
656 investigational product in which all diseases, conditions and physical
657 abnormalities are recorded. A template for health care providers (HCPs)
658 who are not investigators or sub-investigators (for example, the subject's
659 physician, physician assistant, or nurse practitioner) to use in recording
660 and reporting such observations to the investigator may be helpful for such
661 HCPs. Case histories should also include information from scheduled
662 visits with a HCP and test results for persistent vector sequences. The use
663 of surrogate tests may be necessary to indicate vector persistence if direct
664 sequence testing involves an invasive procedure for the subject. If
665 surrogate tests are considered, we recommend that you consult with FDA
666 regarding the types and characteristics of the surrogate tests you intend to
667 use before including them in your study.
668

Contains Nonbinding Recommendations

Draft – Not for Implementation

669 In addition, for the first five years or more (as applicable to your product), we
670 recommend that you do the following:

- 671
- 672 • Assure that investigators maintain, in the case history, a detailed record of
- 673 exposures to mutagenic agents and other medicinal products, and have
- 674 ready access to information about their adverse event profiles.
- 675 • Establish a method for investigators to record the emergence of new
- 676 clinical conditions, including, but not limited to:
- 677 - New malignancy(ies)
- 678 - New incidence or exacerbation of a pre-existing neurologic
- 679 disorder
- 680 - New incidence or exacerbation of a prior rheumatologic or other
- 681 autoimmune disorder
- 682 - New incidence of a hematologic disorder.
- 683
- 684 • Design a plan for scheduled visits with an HCP to elicit and record new
- 685 findings for each study subject, including history, physical examination, or
- 686 laboratory testing.
- 687
- 688 • Such a plan needs to facilitate reporting of delayed adverse events,
- 689 including unexpected illness and hospitalization by study subjects and
- 690 HCPs.

691

692 For the subsequent ten years (applicable to products for which such length LTFU is
693 needed), at a minimum, we recommend that you ensure that your investigators:

- 694
- 695 • Contact subjects at a minimum of once a year. At your discretion, unless
- 696 the LTFU protocol provides for additional specific screening, you may
- 697 arrange to contact subjects by telephone or written questionnaire rather
- 698 than by office visits with an HCP.
- 699
- 700 • Continue appropriate follow-up methods as indicated by previous test
- 701 results. For example, it would be appropriate to monitor for vector
- 702 sequences in subjects who had previous test results demonstrating vector
- 703 persistence.
- 704

705 Perform all LTFU observations according to FDA regulations governing clinical trials
706 (Ref. 27).

707
708

Contains Nonbinding Recommendations

Draft – Not for Implementation

709 We provide additional specific recommendations and requirements for data collection,
710 recording, and reporting of adverse events for LTFU observations as follows:

- 711
- 712 1. Detection of Adverse Events and Coordination of Data Collection
- 713
- 714 a. To facilitate detection of delayed adverse events, we recommend
715 that the LTFU protocol identify suitable HCPs whose observations
716 would be used in the assessment of the occurrence of adverse
717 events in the study population. Suitable HCP might include
718 physicians, physician’s assistants, and nurse practitioners who
719 were not otherwise associated with the clinical trial. You may
720 arrange to have such individuals notified to provide prompt reports
721 of adverse events to the investigators.
- 722
- 723 b. To increase subject compliance and improve the quality of data
724 collection, we suggest that you encourage study subjects to be
725 proactive in reporting adverse events. Tools that study subjects
726 could use to report events to the investigator include subject diaries
727 of health-related events, informational brochures, and laminated,
728 wallet-sized cards with investigator contact information.
- 729
- 730 c. To determine the causality of potential related adverse events (such
731 as tumor formation) associated with your GT product, you should
732 propose a clinical program for follow-up procedures. Such a
733 program would lay out the efforts that would be needed among the
734 study subjects, HCPs, investigators, and the sponsor for study
735 coordination. This includes the collection of tissue samples for
736 follow-up analysis, obtaining informed consent for a biopsy or
737 autopsy (see section V.E. of this document), communicating with
738 the study subject, and preserving and analyzing the tissues/samples
739 according to the LTFU protocol. You may propose specific tests
740 to enable causality analyses such as general blood work,
741 cytogenetic and histological analysis, PCR, HLA typing, or deep
742 sequencing.
- 743
- 744 2. IND Safety Reports
- 745
- 746 You must follow applicable reporting requirements outlined in 21 CFR
747 312.32 for adverse events associated with the use of the investigational
748 product. As the LTFU observations proceed, you must notify FDA and
749 each participating investigator of any serious and unexpected suspected
750 adverse reaction (21 CFR 312.32(c)(1)(i)), and findings from other studies
751 (21 CFR 312.32(c)(1)(ii)). In each IND Safety Report (required to be
752 provided to investigators and FDA), you must identify all safety reports
753 previously filed concerning a similar adverse finding, and analyze the

Contains Nonbinding Recommendations

Draft – Not for Implementation

754 significance of the adverse finding in light of the previous, similar reports
755 (21 CFR 312.32(c)(1)). You must promptly investigate all safety
756 information you receive (21 CFR 312.32(d)(1)). If the relationship of the
757 adverse event to the GT product is uncertain, additional investigations
758 may be needed. You must also revise your informed consent document
759 and Investigator Brochure to include the new adverse event(s) that may be
760 associated with the product or study procedures (21 CFR Part 50, 21 CFR
761 312.55(b)). You must inform all clinical investigators of the newly
762 identified risk (21 CFR 312.32(c)(1)).
763

3. Annual Reports to the IND/Summary Information

764
765
766 While the IND is in effect and LTFU observations are ongoing, you must
767 file an annual report. It is recommended that the annual report contain a
768 subtitle for Long Term Follow-Up (See Appendix 1 of this document). In
769 that report, you should submit information obtained during the previous
770 year's clinical and nonclinical investigations, including, a summary of all
771 IND safety reports submitted during the past year, and a narrative or
772 tabular summary showing the most frequent and most serious adverse
773 experiences by body system (21 CFR 312.33(b)(1) and (2)). If adverse
774 reactions are reported and determined to be related to your product or
775 delivery procedure, you should provide causal analyses based on evidence
776 from clinical, laboratory, molecular, cytogenetic, histological, or HLA
777 analysis, or deep sequencing data. In lieu of annual reports, you may
778 submit a Development Safety Update Report (DSUR). In this case, you
779 should provide the LTFU information in a subsection with a subtitle for
780 LTFU in your DSUR report (Ref. 28).
781

4. Amendments to the Clinical Protocol

782
783
784 If clinical data suggest that your GT product is not associated with delayed
785 risks or there is no evidence of vector persistence, you may want to
786 consider revising the clinical protocol regarding LTFU of study subjects.
787 However, before implementation of this change, we recommend that you
788 consult with FDA and provide your rationale with supporting clinical and
789 laboratory data (we refer you to section V.C of this document for
790 additional guidance). You must submit to FDA a protocol amendment to
791 your IND indicating the relevant changes (21 CFR 312.30(b)(1), (d), and
792 (e)).
793

5. Scheduled Physical Examinations

794
795
796 We recommend that LTFU observations include scheduled physical
797 examinations performed by a HCP once a year during the first five years
798 (or until the completion of LTFU if the LTFU is less than five years),

Contains Nonbinding Recommendations

Draft – Not for Implementation

799 unless the assessed risks associated with your GT product indicate that
800 they should be done more frequently. For example, if a subject exposed to
801 your GT product develops a rapidly progressive, potentially reversible
802 delayed adverse event, and there is a reasonable possibility that the event
803 may have been caused by the product, it may then become advisable to
804 perform observations on a semi-annual or quarterly basis. Such periodic
805 evaluation should include a brief history and focused examination
806 designed to determine whether there is any evidence of emergence of
807 clinically important adverse events. Appropriate laboratory evaluations,
808 such as a hematology profile, should be included with the periodic
809 physical examination. LTFU observations are intended to collect data on
810 delayed adverse events related to the GT product, and are not intended to
811 provide evaluation or treatment data for the underlying disease.
812

6. GT Product Persistence

813
814
815 During LTFU observations, we recommend that you test study subjects at
816 least annually for persistent vector sequences until they become
817 undetectable. More frequent testing may be necessary as outlined in
818 section V.G of this document. The assay should be sufficiently sensitive
819 to detect vector sequences. We recommend that you sample the likely
820 population of transduced cells without being overly invasive (e.g.,
821 peripheral blood is a suitable sample to test for presence of hematopoietic
822 stem cells, rather than bone marrow biopsy). In those cases where
823 collecting the transduced cell population may involve an invasive
824 procedure, we recommend that you consider, instead, measuring a
825 surrogate that may indicate vector persistence (e.g., the level of transgene
826 product or some clinical effect). Data demonstrating the lack of detectable
827 vector may provide a rationale to revise the LTFU protocol as a protocol
828 amendment to your IND. In any such protocol amendment, include an
829 assessment of risks associated with your GT product and an evaluation of
830 the impact of the waning persistence of the vector on those risks (21 CFR
831 312.30(b) and (d)(2)).
832

E. Informed Consent in Trials Involving Long Term Follow-up Observations

833
834
835 Each subject in a clinical investigation must be provided with a description of any
836 reasonably foreseeable risks from participating in the investigation (21 CFR 50.25(a)(2)).
837 The informed consent document must describe, among other things, the purposes of the
838 research, the expected duration of the subject's participation and the procedures to be
839 followed (21 CFR 50.25(a)(1)). Accordingly, the informed consent document must
840 explain the purpose and duration of LTFU observations, the time intervals, and the
841 locations at which you plan to request the subjects to have scheduled study visits or be
842 contacted by other means, and details as to what those contacts will involve (21 CFR
843 50.25).

Contains Nonbinding Recommendations

Draft – Not for Implementation

844
845 When appropriate, the informed consent document must be updated to describe any
846 adverse reactions that may be associated with the product from your trial or other human
847 or animal (preclinical) studies (21 CFR 50.25(b)(5)). If the sponsor intends to store blood
848 or tissue samples for future testing, the informed consent document must convey this
849 information (21 CFR 50.25(a)(1)). The informed consent should also convey that an
850 autopsy may be requested to test vector persistence, transgene expression, and related
851 adverse reactions at the molecular, cellular or tissue level if there are deaths during the
852 LTFU observation. Sponsors must ensure that investigators submit the informed consent
853 documents for Institutional Review Board approval (21 CFR 312.53(c)(1)(vi)(d)).

854
855 We provide additional informed consent recommendations for retroviral vectors in
856 section V.G.3 of this document.

857 858 **F. Special Considerations Regarding Integrating Vectors**

859
860 The recommendations in this section apply exclusively to subjects in clinical trials who
861 received GT products that are integrating vectors, such as transposon elements,
862 gammaretroviral, lentiviral, other retroviral vectors, or GT products that are cells modified
863 *ex vivo* by integrating vectors or transposon-based vectors. See section VI. for post
864 licensure considerations. Because of the risk of developing leukemias and premalignant
865 conditions (clonal cell expansion) due to integration of gammaretroviral vectors and
866 lentiviral vectors (as described in sections III.B and III.C of this document), we are also
867 providing additional recommendations (as listed below) for collection of data in studies
868 in which subjects are exposed to integrating vectors.

869 870 1. Data Collection

871
872 We recommend that you perform assays to assess the pattern of vector
873 integration sites in relevant surrogate cells (e.g., determine whether cells
874 carrying integrated vector sequences are polyclonal, oligoclonal, or
875 monoclonal, with respect to vector integration patterns). We consider an
876 assessment of the vector integration pattern to be relevant in subjects in
877 gene therapy clinical trials involving integrating vectors when: (1) the
878 target cells are known to have a high replicative capacity and long
879 survival, and (2) a suitable surrogate is accessible for assay. For example,
880 hematopoietic stem cells have a high replicative capacity and long
881 survival; peripheral blood could serve as a surrogate for testing for vector
882 persistence if hematopoietic stem cells are the target of your gene therapy.
883 In those cases where peripheral blood is the surrogate, analyses on purified
884 subsets of hematopoietic cells (e.g., lymphocytes vs. granulocytes) may be
885 performed, if deemed appropriate to the study. As an alternative example,
886 if the integrating vector is used for *in vivo* transduction of liver
887 hepatocytes, you may not need to perform this analysis, since terminally
888 differentiated hepatocytes are non-dividing cells under normal

Contains Nonbinding Recommendations

Draft – Not for Implementation

889 circumstances, and there is no reasonable surrogate that allows for non-
890 invasive testing of vector persistence. Please refer to the following
891 recommendations for developing methods and plans for performing these
892 analyses.

- 893
- 894 a. The choice of method to assess the pattern of vector integration
895 sites should be based upon data with appropriate positive and
896 negative controls (i.e., target cells with a known number and sites
897 of vector copies integrated vs. target cells with no vector
898 integrants). Studies should be performed to provide information
899 about the assay sensitivity, specificity, and reproducibility.
 - 900 b. We recommend that you perform an analysis to assess the pattern
901 of vector integration sites if at least 1% cells in the surrogate
902 sample are positive for vector sequences by PCR. As an
903 alternative, you may base the decision to analyze for clonality of
904 vector integration sites on an evaluation of the sensitivity of the
905 assay system used to detect clonality.
 - 906 c. We recommend that you test for vector sequences by PCR in
907 subject surrogate samples obtained at intervals of no greater than
908 six months for the first five years and then no greater than yearly
909 for the next ten years, or until such time that no vector sequences
910 are detectable in the surrogate sample.
 - 911 d. We recommend that you perform an analysis to determine the site
912 of vector integration if the analysis of a subject's surrogate cells
913 suggests a predominant clone (e.g., oligoclonal pattern of vector
914 insertions) or monoclonality. In addition, if you detect a
915 predominant integration site, test for persistence by performing
916 another analysis for clonality no more than three months later.
 - 917 e. When the nucleotide sequence adjacent to the site of the vector
918 integration has been determined, we recommend that you compare
919 the identified integration site sequence with known human
920 sequences in the human genome database and other databases that
921 document oncogenes to determine whether the identified
922 sequences are known to be associated with any human cancers.
 - 923 f. While we recognize that oligoclonality or even monoclonality
924 itself will not a priori result in a malignancy (Refs. 29, 30), we also
925 recognize that these changes increase the risk of a malignancy, and
926 therefore, we recommend that you institute a plan to monitor the
927 subject closely for signs of malignancy if any of the following
928 conditions pertain:
- 929
- 930

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 931
932
933
934
935
936
937
938
939
940
941
942
- i.* Persistent monoclonality;
 - ii.* Clonal expansion (e.g., the percent cells positive for a particular vector integration site is shown to increase over multiple time points); or
 - iii.* Evidence of vector integration near or within a locus known to have oncogenic activity.
- g.* To screen for specific disease entities, we recommend that you use established methods and/or seek advice from clinicians with expertise in screening for the health care risks to which, according to your evidence, your subjects may be exposed.

943 For retroviral (e.g., gammaretroviral and lentiviral) vector-based GT products, additional
944 follow-up monitoring for the presence of replication competent retrovirus (RCR) may be
945 necessary. For details regarding duration of the follow-up monitoring for RCR and
946 methods, please refer to the document “Testing of Retroviral-Based Human Gene
947 Therapy Product for Replication Competent Retrovirus During Product Manufacture and
948 Patient Follow-up; Draft Guidance for Industry” dated July 2018.

949
950 We recommend that GT products with transposon elements should be monitored in a
951 similar way as gammaretroviral or lentiviral vectors. This recommendation is based on
952 the potential safety risk of insertional mutagenesis due to the random integration directed
953 by the transposon, and due to the potential for remobilization of a transposon (secondary
954 transposition-insertion event) as a result of the continuing presence of the transposase
955 enzyme in target cells. Yet, if your GT product contains transposon elements you may
956 propose shorter LTFU observation by providing adequate supporting data/information
957 related to your product.

2. Data Reporting

958
959
960
961 If no evidence of oligoclonality or monoclonality is observed, we
962 recommend that you report a summary of all analyses for the pattern of
963 vector integration sites in narrative or tabular form in the annual report to
964 your IND (21 CFR 312.33(b)(5)). However, if evidence of oligoclonality
965 or monoclonality is observed, you must submit this essential information
966 in an information amendment to the IND (21 CFR 312.31(a)). We
967 recommend that you submit this amendment within 30 days of receiving
968 the report of such an observation.

3. Informed Consent in Trials Involving Retroviral Vectors

969
970
971
972 Please see section V.E for general consideration of LTFU observation
973 informed consent. In accordance with 21 CFR 50.25(a)(2), for all clinical
974 trials in which subjects are exposed to retroviral vectors, the informed
975 consent documents must include current, complete and accurate disclosure

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 976 of the development of leukemias in the clinical trials where such adverse
977 events were reported. Further, the information that is given to the subject
978 or his/her representative must be in language understandable to the subject
979 or representative (21 CFR 50.20). We provide the following list as
980 information and language we recommend be included in the informed
981 consent document, where applicable, in the section describing the risks
982 associated with the study agent:
983
- 984 a. Description of study agent - The study involves giving a person
985 some cells that have been changed by a retroviral vector. A
986 retroviral vector is a virus that can insert genetic material into cells.
 - 987 b. Mechanism of action for retroviral vectors - When retroviral
988 vectors enter a normal cell in the body, the deoxyribonucleic acid
989 (DNA) of the vector inserts itself into the normal DNA in that cell.
990 This process is called DNA integration.
 - 991 c. Effect of DNA integration - Most DNA integration is expected to
992 cause no harm to the cell or to the patient. However, there is a
993 chance that DNA integration might result in abnormal activity of
994 other genes. In most cases, this effect will have no health
995 consequences. However, in some cases, abnormal activity of a
996 gene may cause unpredictable harm such as the development of
997 cancer.
 - 998 d. Discussion of delayed adverse event, leukemia-like malignancy,
999 occurring in human studies - It is important that you know about
1000 some cancers that occurred in another gene therapy research study.
1001 Clinical studies were conducted in France and United Kingdom to
1002 treat a disease called X-linked Severe Combined
1003 Immunodeficiency (SCID). Years after receiving cells that were
1004 modified by a retroviral vector, a significant number of the
1005 children in this small study developed a leukemia-like malignant
1006 disease (cancer). One child died from the cancer. A group of
1007 experts in this field studied the results from tests performed on
1008 these children's blood cells. They concluded that cancer was
1009 caused by the retroviral vector DNA. However, most of the
1010 children with X-linked SCID who have received experimental gene
1011 therapy have not been found to have cancer at this time. Although
1012 they appear healthy, we still do not know whether they, too, will
1013 develop cancer.
 - 1014 e. Risk of malignancy for this study - We do not know if the
1015 retroviral vector used in this protocol might cause cancer.
1016 However, you should be aware that the DNA contained in
1017 retroviral vectors will integrate into your DNA and that under
1018 some circumstances; this has been known to cause cancer months
1019 to years later.
1020

Contains Nonbinding Recommendations

Draft – Not for Implementation

1021 **G. Special Considerations Regarding Product Involving Genome Editing**

1022
1023 While the general principles for LTFU observations of GT products also apply to LTFU
1024 observations of genome editing products, we recommend that you consider the following:

- 1025
- 1026 1. Propose a specific plan to monitor for delayed adverse events based on the
1027 off-target activities noted in your preclinical studies (e.g., *in vivo*, *in vitro*
1028 and *in silico* analysis such as INDEL, (insertion and deletion of bases in a
1029 genome). For example, if the off-target activity involves a tumor
1030 suppression gene in liver cells, you may propose a monitoring plan for
1031 evaluation of occurrence of liver cancer as part of the LTFU observation.
1032
 - 1033 2. Propose a monitoring plan regarding the adverse events from the specific
1034 organ system that the genome editing targets, that may include history and
1035 physical examination, general and specific laboratory tests, and imaging
1036 studies.
1037
 - 1038 3. If direct monitoring of the target tissue is not ethical or feasible, such as,
1039 the brain tissue, you may propose an alternative plan for monitoring of the
1040 product's effects.
1041
 - 1042 4. Quantitate the relationship between the off-target and on-target activities,
1043 and use the measured level of on-target activity to predict the level of off-
1044 target activity and, if appropriate, establish a follow-up plan;
1045
 - 1046 5. If the genome editing product is delivered via systemic administration,
1047 clinical safety monitoring may be directed not only to off-target activity of
1048 the target organ or tissue, but also to other off-target effects that may occur
1049 in other tissues and organs. Accordingly, you may include appropriate
1050 monitoring tests with a rationale for the proposed monitoring in your
1051 LTFU protocol.
1052

1053 1054 **VI. GENERAL CONSIDERATIONS FOR POST-MARKETING MONITORING** 1055 **PLANS FOR GENE THERAPY PRODUCTS**

1056
1057 The number of subjects receiving GT products is typically limited during clinical investigations.
1058 In addition, the recommended LTFU (e.g., 15-year period) will often not elapse for all subjects
1059 who received an investigational GT product in the pre-marketing program before the product is
1060 licensed. Considering that, the safety data generated during clinical trials may not capture all
1061 possible delayed adverse events. Therefore, continuing LTFU observations is often essential
1062 even after a product's licensure. Consequently, we recommend that at the time of your BLA
1063 submission you submit a Pharmacovigilance Plan (PVP) as described in the FDA Guidance for
1064 Industry; E2E Pharmacovigilance Planning (Ref. 31). The contents of PVP for a particular GT
1065

Contains Nonbinding Recommendations

Draft – Not for Implementation

1066 product will depend on its safety profile and will be based on data, which includes the pre-
1067 licensure clinical safety database, published literature, and known product-class effects, among
1068 other considerations.

1069
1070 Routine surveillance for licensed biological products includes adverse event (AE) reporting in
1071 accordance with 21 CFR 600.80 (reporting of expedited and non-expedited AEs as well as
1072 periodic safety reports). Submission of reports for serious, life-threatening and unexpected
1073 adverse events may also be required in an expedited manner beyond routine required reporting.

1074
1075 Additional pharmacovigilance elements may be needed, such as those described in the FDA
1076 Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment; Guidance for
1077 Industry dated March 2005 (Ref. 32), for LTFU of patients treated with GT products. For
1078 instance, we may recommend that you establish a registry to systematically capture and track
1079 data from treated patients with solicited sample collection, and follow-up of adverse events to
1080 resolution or stabilization to collect additional pertinent data. It may be necessary to establish a
1081 registry system to specifically capture adverse event data from treated patients who receive a GT
1082 product. This registry system can be a part of the PVP plan and reviewed at the time of
1083 licensure.

1084
1085 For any proposed or required post-marketing observational studies or clinical trials, we
1086 recommend that you include in your BLA submission the study protocol, statistical analysis plan,
1087 and a projected schedule of anticipated study milestones. Your study protocol should include
1088 specific adverse events of interest that you intend to evaluate, and the duration of observation for
1089 all patients enrolled in your post-marketing study.

1090
1091 During our review of your BLA, we will also assess whether a Risk Evaluation and Mitigation
1092 Strategy (REMS) is necessary to ensure that the benefits of your product outweigh its risks. If
1093 you consider that risk mitigation measures are necessary for the safe use of your product, you
1094 may voluntarily submit your proposed REMS as described in Format and Content of a REMS
1095 Document; Draft Guidance for Industry; Drug Safety dated October 2017 (Ref. 33).

1096
1097
1098 **VII. LONG TERM FOLLOW-UP UNDER SPECIAL CIRCUMSTANCES**

1099
1100 A sponsor may cease to operate or may decide to inactivate, transfer or withdraw an IND before
1101 completion of LTFU observations for all subjects exposed to the GT product under its IND.
1102 Under such circumstances, prior to inactivating, transferring or withdrawing an IND, or ceasing
1103 to operate, we recommend that a sponsor consult with OTAT on the plans for completion of
1104 LTFU observation.

1105
1106
1107

Contains Nonbinding Recommendations

Draft – Not for Implementation

1108 **VIII. DEFINITIONS**

1109

1110 The following definitions apply to this guidance:

1111

1112 **Engineered site-specific endonucleases:** Enzymes that are capable of precisely cleaving
1113 (cutting) DNA based on specific recognition of the DNA sequence at or near the site of DNA
1114 cleavage.

1115

1116 **Genome editing:** The processes by which the genome sequence is changed by adding,
1117 replacing, or removing DNA base pairs using engineered site specific nucleases.

1118

1119 **Gene transfer:** The transfer of genetic material into a cell.

1120

1121 **Human gene therapy:** Human gene therapy seeks to modify or manipulate the expression of a
1122 gene or to alter the biological properties of living cells for therapeutic use.

1123

1124 **Human gene therapy product:** Human gene therapy products are defined as all products that
1125 mediate their effects by transcription or translation of transferred genetic material, or by
1126 specifically altering host (human) genetic sequences. Some examples of gene therapy products
1127 include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi),
1128 engineered site-specific nucleases used for human genome editing⁴, and *ex vivo* genetically
1129 modified human cells.

1130

1131 **Integration (of DNA):** The process whereby exogenous DNA sequences become incorporated
1132 into a genome.

1133

1134 **Latency (of a viral infection):** A period of time during which a virus is present in the host
1135 without producing overt clinical symptoms.

1136

1137 **Maximum feasible dose (MFD) (in preclinical studies):** The highest dose that can be
1138 administered to an animal. Limitations may be due to animal size, administration site, or product
1139 characteristics. The MFD may not be equivalent to the clinically relevant dose.

1140

1141 **Persistence:** With respect to transferred or altered genetic material, the continued presence of
1142 transferred or modified genetic sequences in the host after acute exposure to a gene therapy
1143 agent, whether due to integration of the genetic sequence into the host genome, deletion,
1144 insertion, or otherwise modified following genome editing, or to latent infection with the viral
1145 vector bearing the genetic sequence.

1146

1147 **Reactivation (of a viral infection):** The re-emergence of a symptomatic or asymptomatic viral
1148 infection following a period of latency.

1149

⁴ Human Genome Editing: Science, Ethics, and Governance. The National Academies Press; 2017.
<https://www.nap.edu/read/24623/chapter/1#xvii>

Contains Nonbinding Recommendations

Draft – Not for Implementation

1150 **Transgene:** An exogenous gene that is introduced into a host cell.

1151

1152 **Vector sequences:** Refers to specific sequences of nucleotides, either DNA or RNA, that have
1153 been introduced into a gene therapy product and includes the vector backbone, transgene(s), and
1154 regulatory elements.

1155

1156 **Vector:** A vehicle consisting of, or derived from, biological material that is designed to deliver
1157 genetic material. Examples include plasmids, viruses, and bacteria that have been modified to
1158 transfer genetic material.

1159

Contains Nonbinding Recommendations

Draft – Not for Implementation

1160 IX. REFERENCES

- 1161
- 1162 1. Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed
1163 Adverse Events, November 2006.
1164 [https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryIn](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM078719.pdf)
1165 [formation/Guidances/CellularandGeneTherapy/UCM078719.pdf](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM078719.pdf)
- 1166 2. Human Genome Editing: Science, Ethics, and Governance, National Academy Press,
1167 Washington D.C., 2017.
- 1168 3. Donahue, R.E., et al., Helper virus induced T cell lymphoma in nonhuman primates after
1169 retroviral mediated gene transfer. *Journal of Experimental Medicine* 176:1125-1135, 1992.
- 1170 4. Hacein-Bey-Abina, S., et al., Sustained correction of X-linked severe combined
1171 immunodeficiency by ex vivo gene therapy. *N. Engl. J. Med.* 346: 1185-1193, 2002.
- 1172 5. Biological Response Modifiers Advisory Committee (BRMAC), Meeting Minutes,
1173 Department of Health and Human Services, Food and Drug Administration, CBER, October
1174 10, 2002.
- 1175 6. Biological Response Modifiers Advisory Committee, Meeting Minutes Department of Health
1176 and Human Services (BRMAC), Food and Drug Administration, CBER, November 17,
1177 2000; April 6, 2001; and October 24, 2001.
- 1178 7. Nyberg, K., et al., Workshop on long-term follow-up of participants in human gene transfer
1179 research. *Molecular Therapy* 6:976-980, 2004.
- 1180 8. Hacein-Bey-Abina, S., et al., LMO2-associated clonal T cell proliferation in two patients
1181 after gene therapy for SCID-X1. *Science* 302: 415-419, 2003.
- 1182 9. Hacein-Bey-Abina, S., et al., Insertional oncogenesis in 4 patients after retrovirus-mediated
1183 gene therapy of SCID-X1. *J. Clin Invest* 118: 3132-3142. 2008.
- 1184 10. Braun, et al., Gene Therapy for Wiskott-Aldrich Syndrome—Long term Efficacy and
1185 Genotoxicity *Science Translational Medicine* 6: 227, 2014.
- 1186 11. Cavazzana-Calvo, et al., Gene therapy of human severe combined immunodeficiency
1187 (SCID)-X1 disease, *Science* 288: 669, 2000.
- 1188 12. Howe, et al., Insertional mutagenesis combined with acquired somatic mutations causes
1189 leukemogenesis following gene therapy of SCID-X1 patients. *J Clin Invest* 118: 143-150,
1190 2008.
- 1191 13. Cavazzana-Calvo, et al., Transfusion independence and HMGA2 activation after gene
1192 therapy of human β -thalassaemia. *Nature* 467: 318-322, 2010.
- 1193 14. Cavazzana-Calvo, et al., Haematopoietic stem cell transplantation for SCID patients: where
1194 do we stand? *British Journal of Haematology* 160: 146-152, 2013.
- 1195 15. Niedere, r H.A. and Bangham, C.R.M.; Integration site and clonal expansion in human
1196 chronic retroviral infection and gene therapy. *Viruses* 6: 4140-4164, 2014.
- 1197 16. Sakuma, T., et al., Lentiviral vectors: Basic to translational *Biochem J* 443: 603-618, 2012.
- 1198 17. Maetzig, T. et al., Gammaretroviral vectors: Biology, Technology and Application. *Viruses*
1199 3: 677-713, 2011.
- 1200 18. Aronovich, E., et al., The Sleeping Beauty transposon system: a non-viral vector for gene
1201 therapy. *Hum Mol Genet* 20: R14-R20, 2011.
- 1202 19. Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy,
1203 March 1998,

Contains Nonbinding Recommendations

Draft – Not for Implementation

- 1204 [https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryIn](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM081670.pdf)
1205 [formation/Guidances/CellularandGeneTherapy/UCM081670.pdf](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM081670.pdf)
- 1206 20. Bauer, S., Current FDA approach for preclinical vector biodistribution studies, Recombinant
1207 DNA Advisory Committee Meeting, March 12, 1999.
- 1208 21. Shayakhmetov, D.M., et al., A high-capacity, capsid-modified hybrid adenovirus/adeno-
1209 associated virus vector for stable transduction of human hematopoietic cells. *Journal of*
1210 *Virology* 76(3):1135-1143, 2002.
- 1211 22. Goncalves, M.A., et al., Stable transduction of large DNA by high-capacity adeno-associated
1212 virus/adenovirus hybrid vectors. *Virology* 321(2):287-296, 2004.
- 1213 23. Picard-Maureau, M., et al., Foamy virus—adenovirus hybrid vectors. *Gene Therapy*
1214 11(8):722-728, 2004.
- 1215 24. Yant, S.R., et al., Transposition from a gutless adeno-transposon vector stabilizes transgene
1216 expression in vivo. *Nature Biotechnology* 20(10):999-1005, 2002.
- 1217 25. Wang, Z., et al., Detection of integration of plasmid DNA into host genomic DNA following
1218 intramuscular injection and electroporation. *Gene Therapy* 11(8):711-721, 2004.
- 1219 26. Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of
1220 Cellular and Gene Therapy Products, August 2015,
1221 [https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryIn](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf)
1222 [formation/Guidances/CellularandGeneTherapy/UCM564952.pdf](https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf)
- 1223 27. ICH E6 Good Clinical Practice: Consolidated Guidance, April 1996.
- 1224 28. E2F Development Safety Update Report; Guidance for Industry, August 2011,
1225 [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf)
1226 [es/UCM073109.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf)
- 1227 29. Ott, M.G., et al., Correction of X-linked chronic granulomatous disease by gene therapy,
1228 augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. *Nature Medicine*
1229 12(4):401-409, 2006.
- 1230 30. Schmidt, M., et al., Clonality analysis after retroviral-mediated gene transfer to CD34+ cells
1231 from the cord blood of ADA-deficient SCID neonates. *Nature Medicine* 9(4):463-468, 2003.
- 1232 31. E2E Pharmacovigilance Planning; Guidance for Industry, April 2005,
1233 [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf)
1234 [s/ucm073107.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf).
- 1235 32. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic
1236 Assessment, March 2005,
1237 [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696.pdf)
1238 [es/UCM071696.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071696.pdf)
- 1239 33. Format and Content of a REMS Document; Draft Guidance for Industry; Drug Safety,
1240 October 2017,*
1241 [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidanc](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf)
1242 [es/UCM184128.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf)

1243
1244
1245
1246
1247
1248

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

1249
1250
1251
1252
1253

APPENDICES

APPENDIX 1: INFORMATION FOR LONG TERM FOLLOW-UP (LTFU) OBSERVATION ANNUAL REPORT

Category	Required LTFU Data	Rationale
Protocol Title	“Long Term Follow-Up Observation Annual Report”	The placement of this title will facilitate FDA to search for LTFU data in our database
LTFU Protocol Status	Total length (years) Starting date Total number of subjects enrolled Subjects that have completed LTFU observation Remaining subjects on LTFU observation	This will serve as a brief summary.
Product Information	Vector persistence Clonality analyses RCR On and off-target analyses for products that involve genome editing	This is the focus of the product safety assessment in the LTFU protocol and provides important information for monitoring, and for determination of the length of the LTFU observation.
Preclinical Information	New preclinical data Relevant findings from the literature	This provides data and signals to guide the direction of LTFU observation.
Clinical Information	Any related delayed adverse event with brief narrative Oncological, neurological, hematological, auto-immune or other disorder Causal analyses based on evidence from clinical, laboratory, molecular, cytogenetic, histological, HLA analysis, deep sequencing data Serious adverse events Evidence for persistence of the product/therapeutic protein/sequences, and durability of the clinical effects	This is the focus of the product safety assessment in LTFU observation, and serves as a guide for the types of AE, organ systems, and methodology to attribute AE/Serious Adverse Event (SAE) to the GT product. The durability of clinical effect also allows for an assessment of product efficacy in the LTFU observation report, but inclusion of such data is at the sponsor’s discretion.
Revision of LTFU protocol	Rationale for modifying LTFU observation FDA agreement to revised LTFU protocol: synopsis of meeting(s) discussion/email communication Discussion and date of discontinuation	This will provide an opportunity for revising the content and length of the LTFU observation based on data collected in the studies or other relevant information.

1254
1255
1256
1257

Contains Nonbinding Recommendations

Draft – Not for Implementation

1258 **APPENDIX 2: SAMPLE TEMPLATE: LONG TERM FOLLOW-UP (LTFU)**
 1259 **OBSERVATION ANNUAL REPORT**

Category	List of LTFU data	Annual reporting
Protocol title	“Long Term Follow-Up Observation Annual Report”	[product name]: LTFU2017 annual report for protocol [#]
LTFU protocol status	Total length (years):	15 years
	Starting date:	October 30, 2009
	Total number of subjects enrolled:	30
	Subjects that have completed LTFU observation:	0
	Remaining subjects on LTFU observation:	20 (2 deaths, 5 lost to flu, 3 drop outs)
Product information	Vector persistence:	PCR ¹ of [name] transgene positive in 17 of 20 subjects still on study at 5 yrs and 3 subjects at 7 yrs.
	Clonality analyses:	No clones more than 1% for more than 1 testing period
	RCR	ND ² , request to discontinue RCR testing
	On and off-target analyses for products that involve genome editing	NA ³
Preclinical information	New preclinical data	Final study report for large reproductive toxicity study in normal SD rats (study report [#]). Published in [journal citation]. No additional studies ongoing at this time.
	Relevant findings from the literature	No new literature on [x] disease at this time.
Clinical information	Any related delayed adverse event with brief narrative	One case of rash that resolved with steroids. No other symptoms. PCR of rash biopsy was negative for vector.
	Oncological, neurological, hematological, auto-immune or other disorder	Secondary tumor on left ear, negative for vector sequences by PCR. Unrelated, melanoma.

Contains Nonbinding Recommendations

Draft – Not for Implementation

	Causal analyses based on evidence from clinical, laboratory, molecular, cytogenetic, histological, HLA analysis, deep sequencing data	NA
	Serious adverse events	2 deaths due to sepsis, related to underlying disease. No other unexpected SAE reported
	Evidence for persistence of the product/therapeutic protein/sequences, and durability of the clinical effects	20 subjects are still on study with vector persists in BM and PBMC samples, and clinical benefit observed. All twenty subjects have reconstituted immune system, with some b cell aphasia and low platelet counts in three subjects, however no transfusions needed to date.
Revision of LTFU Protocol	Rationale for modifying LTFU observation	All RCR testing results negative (n=150 samples). Risk assessment determined very low risk of RCR developing in subjects at this time.
	FDA agreement to revised LTFU protocol: synopsis of meeting(s) discussion/email communication	Revision to LTFU discussed during pre-BLA meeting [date]. RCR testing will no longer performed for LTFU protocol [#]
	Discussion and date of discontinuation	NA

1260 ¹ polymerase chain reaction

1261 ² none detected (ND)

1262 ³ not applicable (NA)