

Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

Draft Guidance for Industry

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**U.S. Department of Health and Human Services
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I. INTRODUCTION

The management of manufacturing changes presents many challenges for human cellular therapy¹ or gene therapy² (CGT) products due to the complexity of these products. We, FDA, are providing you, sponsors of Investigational New Drug Applications (INDs) and applicants of Biologics License Applications (BLAs) for CGT products, with recommendations regarding product comparability and the management of manufacturing changes for investigational and licensed CGT products.³ The purpose of this guidance is to provide FDA’s current thinking on 1) management and reporting of manufacturing changes for CGT products based on a lifecycle approach, and 2) comparability studies to assess the effect of manufacturing changes on product quality.^{4, 5}

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only

¹ For the purposes of this guidance “cellular therapy products” include certain tissue-engineered medical products (referred to in this guidance as TEMPs) that contain living cells (see section VI of this guidance) and are regulated under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262).

² Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids, genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells.

³ Cellular and gene therapy products meet the definition of “biological product” in section 351(i) of the PHS Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), <https://www.fda.gov/media/76647/download>).

⁴ This guidance does not apply to vaccines for infectious disease indications, bacteriophage products, live biotherapeutic products, fecal microbiota for transplantation (FMT) products and allergenic products.

⁵ For the purposes of this guidance, the term “product quality” refers to identity, strength, quality, purity, and potency of a product, as these factors may relate to the safety or effectiveness of the product.

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28 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
29 the word *should* in Agency guidances means that something is suggested or recommended, but
30 not required.

31

32

33 **II. BACKGROUND**

34

35 CGT products are regulated under the existing framework for biological products.
36 Manufacturing and control of CGT products can often be affected by unique factors, including
37 limited knowledge of product quality attributes, limited manufacturing experience, limited and
38 variable starting materials, limited amount of product, complex manufacturing processes, and
39 limited product shelf life. These aspects of CGT products may make the management of
40 manufacturing changes more challenging than for other biological products.

41

42 A CGT product manufacturer may seek to implement a manufacturing change for a variety of
43 reasons, including improving product quality, expanding product supply, or improving
44 manufacturing efficiency. The risk that a manufacturing change may adversely impact product
45 quality should be prospectively assessed under the manufacturer’s quality risk management
46 processes (Refs. 1, 2). We note that while improvement of product quality is always desirable
47 and encouraged, if the results of comparability studies indicate an improved product quality
48 suggesting a significant benefit in effectiveness and/or safety, the pre- and post-change products
49 may be different products and, therefore, not comparable.

50

51 Risk assessment should be performed for all types of manufacturing changes, regardless of the
52 stage of product development. If a risk assessment indicates that a manufacturing change has the
53 potential to adversely affect product quality, comparability studies should be performed to
54 evaluate the impact of the proposed manufacturing change. It can be difficult to fully
55 characterize CGT products using analytical methods, and in some cases analytical studies alone
56 may not be sufficient to reach a conclusion regarding comparability. In such cases, additional
57 data from nonclinical studies may help to support comparability. Otherwise, additional clinical
58 studies may be warranted.

59

60 The extent of analytical evaluation needed to adequately evaluate a manufacturing change in
61 comparability studies generally increases with the stage of clinical and product development and
62 should be supported by knowledge of critical quality attributes (CQAs) (Ref. 3), accumulated
63 manufacturing experience, and further understanding of the mechanism of action (MOA). For
64 both licensed and investigational products, assessing the risks of manufacturing changes is
65 essential before designing comparability studies. For licensed products, applicants are required
66 to assess the effects of “each change in the product, production process, quality controls,
67 equipment, facilities, responsible personnel, or labeling established in the approved license
68 application(s)” (Title 21 of the Code of Federal Regulations (CFR) 601.12(a)(1)-(2)).⁶
69 Applicants must also demonstrate through appropriate validation and/or other clinical and/or

⁶ For purposes of this guidance, the term “manufacturing change” in the context of a licensed product, refers to a change (other than a labeling change) that would fall within the types of changes described in 21 CFR 601.12(a)(1).

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70 nonclinical laboratory studies that each manufacturing change does not adversely affect product
71 quality before distributing a product manufactured using the change (21 CFR 601.12(a)(2)). For
72 investigational products, sponsors must provide sufficient chemistry, manufacturing, and control
73 (CMC) information to assure product safety, identity, quality, purity, and strength (including
74 potency) of the product (21 CFR 312.23(a)(7)(i)), and some manufacturing changes without
75 adequate comparability data may result in a clinical hold (21 CFR 312.42(b)).

76
77 The guidance entitled “Demonstration of Comparability of Human Biological Products,
78 Including Therapeutic Biotechnology-derived Products” dated April 1996 (Ref. 4) contains
79 general recommendations applicable to biological products, but it does not address the specific
80 challenges of performing comparability studies with CGT products. The guidance entitled “Q5E
81 Comparability of Biotechnological/Biological Products Subject to Changes in Their
82 Manufacturing Process” dated June 2005 (Ref. 5) contains principles that may be useful for
83 comparability studies of CGT products. However, its scope is limited to certain proteins and
84 polypeptides that can be highly purified and characterized, which are typically less complex,
85 better characterized, and manufactured to more stringent tolerances than CGT products. Other
86 FDA guidance documents related to management of manufacturing changes and risk
87 management for biological products generally do not address specific CGT product challenges
88 (e.g., Refs. 1, 2, 6). The purpose of this guidance is to provide recommendations for managing
89 manufacturing changes and assessing comparability for both investigational and licensed human
90 CGT products while considering the unique challenges that apply to these products.

91

92

93 **III. CONSIDERATIONS FOR THE MANAGEMENT OF MANUFACTURING** 94 **CHANGES**

95

96 An effective quality system maintains consistency in drug product (DP) quality throughout the
97 product lifecycle, including by adequately managing manufacturing changes. In general,
98 manufacturing changes should be thoroughly assessed and documented using effective change
99 control procedures. For investigational products, maintaining product quality by control of
100 CQAs and critical process parameters (CPPs) during manufacturing changes is important for
101 obtaining interpretable clinical study data that can support licensure. A robust framework for
102 managing manufacturing changes is especially valuable for CGT products because of the
103 complexity of these products and their manufacturing processes.

104

105 **A. Risk Management**

106

107 Managing manufacturing changes can be challenging for CGT products due to difficulty
108 in identifying risks to product quality and uncertainty about how to mitigate risk.
109 Therefore, we recommend that you apply a systematic approach to quality risk
110 management designed to identify, assess, analyze, and mitigate potential risks. Such an
111 approach can facilitate science-based decision-making and enable a risk-based evaluation
112 of manufacturing changes (Ref. 1).

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114 Defining acceptable ranges for CQAs and establishing operating ranges for CPPs prior to
115 making a manufacturing change facilitates conducting a risk assessment and evaluating
116 the change. For example, for a cellular product that has a manual wash step, it would
117 generally be easier to transition to an automated wash process if the acceptable operating
118 range for the duration of the cell washes has already been established, because this
119 parameter can impact product CQAs and process performance.

120 Factors such as product and process knowledge, qualification/validation of methods, and
121 the stage of clinical development should be considered when assessing the risk of the
122 manufacturing change. In particular, you should carefully assess risks to product quality
123 if extensive manufacturing changes are introduced shortly before BLA submission. In
124 such a situation, a comparability study should be comprehensive and should provide high
125 confidence that the change does not adversely impact product quality (section V of this
126 guidance). Additionally, introducing a manufacturing change at this late stage of
127 development or after licensure could require additional process performance qualification
128 studies if the existing qualification study is not representative of the intended commercial
129 process (e.g., 21 CFR 211.22, 211.100, 211.110(a) and 211.165). For a process that has
130 already been validated, you should also determine whether there is a need for any
131 changes to the plans for continued process verification as a result of the manufacturing
132 change (Ref. 7). For these reasons, we recommend that any extensive manufacturing
133 changes be introduced prior to initiating clinical studies that are intended to provide
134 evidence of safety and effectiveness in support of a BLA.
135

136 To facilitate manufacturing changes during rapid clinical development, CGT product
137 manufacturers should ensure that the pace of product development is aligned with the
138 stage of clinical development. For example, if you initiate clinical studies using product
139 generated by a manufacturing process designed with a potential for scalability, this will
140 help decrease the likelihood of delays later in clinical development when the
141 manufacturing process is scaled up.
142

143 For both investigational products subject to 21 CFR part 211 and licensed products, you
144 must evaluate data at least once a year to determine if changes in product specifications
145 or manufacturing or control procedures are needed to maintain the quality standards of
146 the product, even when no manufacturing changes are undertaken (21 CFR 210.2,
147 211.180(e) and 601.2(d)). Data trend analysis throughout product development can also
148 be useful for verifying that manufacturing changes do not lead to shifts in manufacturing
149 consistency over time.
150

B. Stability and Delivery Device Compatibility

151
152
153 Product stability may be adversely affected by manufacturing changes, including changes
154 made during processing, holding steps for intermediates, and shipping or storing the drug
155 substance (DS) or DP. CGT products are often sensitive to storage and handling
156 conditions. DP stability should be thoroughly assessed after changes to the container
157 closure system, formulation, product concentration, or shipping conditions.

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158 Manufacturing changes to CGT products may also have the potential to affect
159 compatibility of the DP with delivery devices.

160
161 When evaluating the risk of a manufacturing change, we recommend that you determine
162 if there is a need to perform stability and/or delivery device compatibility studies to
163 assess the effect of the change on product quality, and whether any such studies should
164 evaluate in-process material, DS, or DP. Stability studies should focus on the evaluation
165 of stability-indicating quality attributes. The stability testing plan should define
166 appropriate acceptance criteria, which may be different from the acceptance criteria for
167 release of the product.

168
169 Many CGT products are stored frozen for a significant length of time. Accelerated stability
170 studies performed under stress conditions may be useful for identifying stability-indicating
171 attributes, but shelf life should be based on real-time stability data obtained at the long-term
172 storage condition. Generating real-time long-term stability data can delay product
173 development, especially when manufacturing changes that have the potential to adversely
174 affect stability are implemented during late stages of product development. For post-licensure
175 manufacturing changes, there may be a need to generate real-time stability data with the post-
176 change product to demonstrate a lack of adverse effect on product quality, and generating these
177 data could severely delay the implementation of the manufacturing change.

178 179 **C. Nonclinical studies**

180
181 Nonclinical studies may be needed to support manufacturing changes for an
182 investigational product after clinical studies have been initiated (Ref. 8), or for a licensed
183 product (21 CFR 601.12(a)(2)). If analytical studies alone are insufficient to determine
184 the impact of the manufacturing changes on CGT product quality, then nonclinical
185 studies may contribute to a demonstration of comparability.

186 187 **D. Clinical studies**

188
189 We recommend that comparability of investigational or licensed CGT products be
190 evaluated through analytical assessment and, if appropriate, nonclinical studies. When
191 applicable and feasible, studies evaluating pharmacokinetic/pharmacodynamic (PK/PD)
192 parameters may be used to contribute evidence in support of comparability between the
193 pre- and post-change products. When comparability cannot be established through
194 analytical, nonclinical, and/or PK/PD studies, the evidence of safety and effectiveness
195 accumulated during clinical investigation with the pre-change product will be insufficient
196 to support a BLA for the post-change product, and the sponsor should contact FDA to
197 discuss plans for additional clinical investigations of the safety and/or effectiveness of the
198 post-change product.

199
200 *Investigational Products*

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202 If analytical and/or nonclinical comparability studies are insufficient to assure that a
203 manufacturing change will not adversely affect safety, then the sponsor should discuss
204 with the FDA (section VII of this guidance) their plans for safety evaluation of the post-
205 change product, which may include conducting new clinical studies and/or incorporating
206 additional safeguard measures and safety evaluations in ongoing clinical studies. For
207 example, it may be appropriate to consider broadening the scope of the adverse events of
208 special interest, staggering enrollment of subjects, modifying study stopping rules, and
209 conducting additional dose-finding studies.

210
211 If comparability studies demonstrate that the manufacturing change does not adversely
212 affect product safety but are insufficient to exclude an adverse impact on product
213 effectiveness, then the sponsor will need to evaluate the effectiveness of the post-change
214 product in clinical studies to support a BLA for the post-change product.

215
216 It is important to critically evaluate any manufacturing change that has the potential to
217 affect product effectiveness when the change is proposed after initiation of studies
218 intended to provide substantial evidence of effectiveness in support of a BLA. In
219 addition, evidence demonstrating a prospect of direct benefit of a pre-change
220 investigational CGT product to pediatric subjects, as required for studies conducted in
221 accordance with 21 CFR 50.52, may not be adequate to demonstrate prospect of direct
222 benefit with respect to the post-change product. If comparability cannot be established
223 between the pre- and post-change product, the sponsor should discuss with the FDA
224 (section VII of this guidance) any proposed modifications to the clinical development
225 program for the post-change product. Such modifications could include an increase in
226 the number of subjects exposed to the post-change product and initiation of new clinical
227 studies with the post-change product. In the case of pediatric studies for which a prospect
228 of direct benefit is required, nonclinical data demonstrating prospect of benefit may be
229 sufficient during early-stage clinical development.

230
231 If you wish to pool clinical data from subjects treated with the post-change product and
232 subjects treated with the pre-change product, you should demonstrate that the products
233 are comparable and justify that the clinical study designs are appropriate for pooling. We
234 also recommend that you seek FDA's advice (section VII of this guidance) on the design
235 of the pooled data analysis, preferably before conducting late-phase studies intended to
236 demonstrate product effectiveness in support of a BLA.

237
238 *Licensed Products*

239
240 If analytical and/or nonclinical comparability studies are unable to demonstrate that a
241 manufacturing change to a licensed product has no adverse effect on product quality,
242 FDA will not be able to approve the manufacturing change based on those studies (21
243 CFR 601.12). In such cases, we recommend that you discuss alternative approaches with
244 the FDA (section VII of this guidance), which will be evaluated on a case-by-case basis.
245 For example, you may consider initiating new clinical studies with the post-change
246 product under an IND to obtain evidence of its safety and effectiveness.

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247 **IV. REGULATORY REPORTING OF MANUFACTURING CHANGES**

248
249 IND sponsors must notify FDA of manufacturing changes through an amendment if
250 manufacturing information previously submitted no longer accurately reflects the current state of
251 manufacturing because essential information is missing (21 CFR 312.31(a)(1)). Applicants must
252 notify FDA of manufacturing changes through a BLA supplement or annual report in accordance
253 with 21 CFR 601.12 (Ref. 6). When submitting an IND amendment or a BLA supplement for a
254 manufacturing change, your cover letter should clearly describe the purpose of the amendment
255 and highlight proposed changes (Ref. 9). For amendments containing extensive changes, we
256 recommend that you provide a “Reviewer’s Guide” or a comprehensive summary of the changes
257 in Common Technical Document (CTD) sections 1.2 or 1.11.1, respectively.⁷ Module 3 and any
258 other relevant sections of the IND or BLA should be modified to include the change, and the
259 developmental history of the manufacturing process should be updated in the pharmaceutical
260 development sections (3.2.S.2.6 and 3.2.P.2.3) of your IND or BLA. The type of submission,
261 timing of submission, and amount of information required in the submission will vary depending
262 on the stage of product and clinical development and the nature of the manufacturing changes, as
263 described further below.

264 **A. CMC Changes Requiring a New IND Submission**

265
266
267 Some changes can fundamentally alter the design or nature of the product, resulting in a
268 new product. Initiation of clinical studies with the new investigational product generally
269 requires the submission of a separate IND (21 CFR 312.20). We recommend that you
270 seek FDA advice (section VII of this guidance) regarding any manufacturing changes that
271 could alter the product and require a new IND. Some examples of changes that may
272 require a new IND include:

- 273 • Change in the cellular starting material of a cellular product (e.g., allogeneic vs.
274 autologous donor; adipose-derived cells vs. umbilical cord-derived cells)
- 275 • Change to the types of cells in a cellular product (e.g., mixture of CD4⁺ and CD8⁺
276 T cells instead of solely CD4⁺ T cells)
- 277 • Change to the scaffold or matrix component of the final construct in a TEMP
278 (e.g., changes to chemical or physical properties) causing significant modification
279 to the product characteristics
- 280 • Change in a viral vector capsid or envelope that changes the tropism or serotype
281 of a viral vector used for in vivo gene therapy
- 282 • Change to the sequence of a transgene or addition of a transgene (e.g., changes to
283 the intracellular signaling domain of a chimeric antigen receptor)
- 284 • Change in expression control elements of a viral vector (e.g., change from a
285 tissue-specific to a ubiquitous promoter)
- 286 • Change of target gene for genome editing products, including addition of a target
287 gene

⁷ For information on electronic CTD (eCTD) submission requirements, please see the FDA website
<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd>.

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288 **B. Reporting Manufacturing Changes to an IND**

289
290 FDA regulations require all sponsors of investigational new drug products, including
291 investigational CGT products, to describe the CMC information for the DS (21 CFR
292 312.23(a)(7)(iv)(a)) and the DP (21 CFR 312.23(a)(7)(iv)(b)). The CMC information in
293 your IND must be sufficient to assure the safety, identity, quality, purity, and strength
294 (including potency) of the investigational product (21 CFR 312.23(a)(7)(i)). The CMC
295 information in an IND describes a sponsor's commitment to perform manufacturing and
296 testing of the investigational product as stated in the IND or in a cross-referenced IND or
297 master file. If a manufacturing change could affect product quality, we consider the
298 manufacturing change essential information that must be submitted in an information
299 amendment to the IND (21 CFR 312.31(a)(1)). The sponsor should submit such
300 amendments for FDA review prior to use of the changed product in clinical
301 investigations. The FDA will review data or study reports submitted to support the
302 change, and may provide comments (section V of this guidance). In addition, each year
303 you must submit an annual report that provides a summary of any significant
304 manufacturing changes made during the past year (21 CFR 312.33(b)(7)).
305

306 If a manufacturing change has the potential to adversely affect safety, and if you do not
307 submit evidence to your IND demonstrating that the post-change product has an
308 acceptable safety profile, then your IND may be placed on clinical hold at any phase of
309 clinical development (21 CFR 312.42(b)(1)(i), 21 CFR 312.42(b)(1)(iv), and 21 CFR
310 312.42(b)(2)(i)). Evidence may be provided as an amendment to the IND in the form of
311 analytical comparability data or other analytical data relevant to safety. If these data do
312 not allow for a conclusive determination that the manufacturing change has no adverse
313 effect on product quality as it relates to safety, then you should consider performing a
314 toxicology study to evaluate whether the post-change product has an acceptable safety
315 profile.
316

317 If you make a manufacturing change that has the potential to adversely impact the
318 effectiveness of the product without submitting evidence to your IND demonstrating that
319 the post-change product is comparable to the pre-change product, this may also result in a
320 clinical hold for certain clinical studies (21 CFR 312.42(b)). FDA's review of an IND
321 submission for a phase 2 or 3 clinical study includes assessing the likelihood that the
322 study will yield data capable of meeting statutory standards for marketing approval (21
323 CFR 312.22(a)), and a phase 2 or 3 study may be placed on clinical hold if the plan or
324 protocol for the study is clearly deficient in design to meet its stated objectives (21 CFR
325 312.42(b)(2)(ii)). If, for example, a phase 3 study intended to provide substantial
326 evidence of effectiveness to support a BLA for a post-change product uses lots of both
327 pre- and post-change product, but those products are not comparable, then the study may
328 lack statistical power to demonstrate effectiveness of the post-change product. Such a
329 study may be considered clearly deficient in design to meet its stated objectives and
330 placed on clinical hold if the IND submission does not provide evidence demonstrating
331 comparability of the pre- and post-change products.
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333 In addition, FDA may place studies on clinical hold if subjects would be exposed to an
334 unreasonable and significant risk of illness or injury (21 CFR 312.42(b)(1)(i) and
335 312.42(b)(2)(i)). If you make a manufacturing change that could adversely affect the
336 effectiveness of the investigational product without demonstrating comparability, then the
337 capacity of the post-change product to provide a potential benefit to subjects may be in
338 doubt. This may lead to a conclusion that a significant risk of illness or injury involved
339 in a clinical investigation is unreasonable, and the study may be placed on clinical hold.

340 **C. Reporting Manufacturing Changes to a BLA**

341
342 For licensed products, you must report each change in the product, production process,
343 quality controls, equipment, facilities, responsible personnel, or labeling established in
344 the approved license application, in accordance with the requirements in 21 CFR 601.12.
345 When reporting these changes, your supplement or annual report should include a risk
346 assessment report and must include data from appropriate studies performed to evaluate
347 the effect of the changes on product quality as required under 21 CFR 601.12(b)(3)(iv)-
348 (v), 21 CFR 601.12(c)(3), or 21 CFR 601.12(d)(3)(ii) (Ref. 6).

350
351 To facilitate management of post-approval manufacturing changes, you may submit one
352 or more comparability protocols to your BLA for FDA review, as described in 21 CFR
353 601.12(e). These protocols may be submitted either in the original BLA or, if the
354 application is already approved, in a prior approval supplement (Ref. 10). Comparability
355 protocols should be located in section 3.2.R of your BLA. Upon approval, this protocol
356 becomes an agreed-upon plan for implementation of the manufacturing change using the
357 reporting category specified in the approved comparability protocol submitted under 21
358 CFR 601.12(e), provided that there is successful completion of the plan for
359 implementation of the change(s) as described in the comparability protocol (including
360 achievement of all of the predefined acceptance criteria for success in the approved
361 comparability protocol) (Ref. 10).

362 363 364 **V. COMPARABILITY ASSESSMENT AND REPORT**

365
366 Comparability between the pre-change and post-change products is generally demonstrated by
367 evidence that the change does not adversely affect product quality for the licensed (21 CFR
368 601.12(a)(2)) or investigational product. However, if the change is intended to improve product
369 quality, such that there is a significant benefit in effectiveness and/or safety, then the post-change
370 product may be considered a different product, and therefore not comparable to the pre-change
371 product. We recommend that you seek FDA advice (section VII of this guidance) when planning
372 significant manufacturing changes and when designing study protocols for comparability studies.
373 Section V of this guidance describes considerations for designing a comparability study,
374 analyzing comparability data, and submitting a comparability study report. For information on
375 reporting manufacturing changes to FDA, please refer to sections IV.B of this guidance for
376 reporting changes to an IND and section IV.C of this guidance for reporting changes to a BLA.

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377 When submitting a comparability study report to an IND or BLA, you should include a cover
378 letter or reviewer’s guide outlining the submission contents to streamline the FDA review
379 process. In the cover letter or reviewer’s guide, you should provide a description of the proposed
380 change, rationale for the proposed change, proposed timeline for implementing the change, and
381 justification for the design of the comparability study. Further, to aid FDA review of your study,
382 we recommend that you provide a short summary of your current relevant manufacturing and
383 clinical experience. When submitting a comparability study report to your IND, for example, it
384 is helpful to describe the stage of clinical development, the number of subjects to whom the pre-
385 change product will be administered, and the number of subjects expected to receive the post-
386 change product. You should provide a summary of relevant previous manufacturing changes and
387 their effect on process consistency and product quality. You should also note any previous
388 changes made to product specifications (for DP, DS, and key intermediates) and provide a
389 description of any CQAs for which an analytical method is still under development.

390
391 Comparability study reports should be submitted to CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the
392 BLA or IND, as appropriate. Your comparability study report should evaluate the totality of the
393 comparability data, including historical manufacturing data, to determine if the pre- and post-
394 change products are comparable. We recommend that you summarize the findings of the
395 comparability study and discuss how the data and analyses support your conclusion from the
396 study. You should also include a discussion of any potential limitations of the study. If a
397 product quality attribute does not meet the pre-defined acceptance criterion for comparability,
398 but you still consider the pre- and post-change products to be comparable, you should provide
399 justification and/or additional scientific information to support your conclusion for FDA review.

400 401 **A. Risk Assessment**

402
403 Manufacturing changes that can present potential risk to product quality include, but are
404 not limited to, changes to the manufacturing site, manufacturing process, materials,
405 container closure, testing, storage, and shipping conditions. To evaluate whether the
406 proposed manufacturing change may impact product quality, you should conduct a
407 detailed risk assessment as recommended in International Council for Harmonisation
408 (ICH) Q9 dated June 2006 (Ref. 1). The process of evaluating the risk of a
409 manufacturing change for a CGT product is similar to risk evaluation for other types of
410 drugs, and the same tools can generally be applied.

411
412 We recognize that risk assessment for changes to the manufacturing of CGT products
413 may be more challenging than for other product types because the effects of
414 manufacturing changes are often difficult to predict for these complex products. For
415 example, manufacturing changes may unexpectedly alter product purity (increase
416 process-related impurities, cellular impurities, aggregates, or particulates), reduce product
417 stability, or change product potency.

418
419 Transferring a manufacturing process to a new manufacturing facility is generally
420 considered a major change that may require extensive comparability evaluation in
421 addition to technology transfer, because it may involve changes to the manufacturing

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422 process, shipping, manufacturing equipment, testing equipment, and operators.
423 Performing a thorough risk assessment, including consideration of method equivalence
424 and CPPs, is essential when transferring a manufacturing process to a new facility.
425

426 Your risk assessment should consider potential impacts of the change on the
427 manufacturing steps and in-process parameters that are downstream of the manufacturing
428 change, as well as the impact on the product. We recommend that you take a stepwise
429 approach to select all quality attributes and process parameters to be evaluated in a
430 comparability study; first, you should determine which attributes might be affected by the
431 particular change, and then you should assign a score to each attribute based on the
432 probability, severity, and detectability of the risk. The assigned score can be used to
433 determine the overall risk for each attribute. Manufacturing changes that are determined
434 to have a high risk to product quality should be supported by an extensive analytical
435 comparability study, while it may be possible to evaluate low-risk changes using a more
436 focused approach.
437

438 You should consider whether your risk assessment is constrained by gaps in product
439 knowledge related to the type of change being proposed. Gaps in knowledge typically
440 raise the level of risk and may necessitate a more extensive comparability study. Please
441 note that relying solely on established release tests and in-process controls is generally
442 insufficient to assess the impact of manufacturing changes. Therefore, we recommend
443 that you consider the potential impact of manufacturing changes on quality attributes that
444 are not routinely evaluated by established release tests and process controls, and consider
445 additional characterization studies as appropriate. Additionally, your risk assessment
446 should evaluate whether more than one analytical method should be used to evaluate a
447 particular attribute. Such an approach could be useful for high-risk attributes, particularly
448 with respect to assessment of potency, as described in section V.B of this guidance. In
449 your risk assessment, you should justify how the selected quality attributes and process
450 parameters can be used to comprehensively evaluate the potential effect of the change on
451 product quality.
452

453 Your risk assessment should also inform the statistical approach to comparability.
454 Higher risk attributes typically warrant a more stringent statistical analysis than lower
455 risk attributes. Side-by-side or graphical presentations (such as dot plot) to allow visual
456 comparison, in lieu of statistical analysis, may be sufficient for characterization of
457 attributes at low risk of being impacted by a manufacturing change.
458

459 It is important to note that a manufacturing change may affect product stability even if
460 the change has no other effect on product quality or process performance. As discussed
461 in section III.B, you should assess the potential risk to product stability and delivery
462 device compatibility.
463

464 Finally, if multiple changes are to be implemented simultaneously, we recommend that
465 you assess the risk of each individual change and the potential cumulative effect of the
466 changes on product quality. It may be possible to evaluate these multiple changes under

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467 a single comparability study. However, if you fail to demonstrate comparability in this
468 single study, it will likely be difficult to identify which of the changes caused an adverse
469 effect on product quality.

470

471 **B. Analytical Comparability Study Design**

472

473 It is essential that a comparability study be sufficiently robust to reach a definitive
474 conclusion regarding comparability. Therefore, it is important to carefully select relevant
475 quality attributes, analytical methods, acceptance criteria, and statistical methods. Prior
476 to conducting a comparability study for a CGT product that is licensed or being studied
477 under an IND, we recommend that you submit a detailed study protocol (comparability
478 protocol) and request feedback from the FDA (section VII of this guidance) on the study
479 design and statistical approach. As noted above, the regulations also provide for
480 applicants to submit and seek FDA approval of a comprehensive, prospectively written
481 plan for assessing the effect of a proposed post-approval manufacturing change(s) on
482 product quality (21 CFR 601.12(e) and Ref. 10). These comparability protocols can be
483 submitted in an original BLA or in a prior approval supplement (21 CFR 601.12(e)).

484

485 The extent of a comparability study should be driven by the conclusions from the risk
486 assessment, which should inform your selection of: 1) a relevant set of quality attributes
487 to measure the effect of the manufacturing change on product quality, 2) appropriate test
488 methods, and 3) comparability acceptance criteria that are adequate to demonstrate a lack
489 of adverse effect of the manufacturing change on product quality, as discussed later in
490 this section. To adequately evaluate the impact of the manufacturing change on product
491 quality, a comparability study will frequently need to include measurement of attributes
492 that are not routinely used for product release.

493

494 We recommend that you consider the following factors when designing a comparability
495 study:

496

497 *Selection of product lots for the study*

498

499 A comparability study should generally be performed using lots that have been
500 manufactured at full scale. Experience with smaller scale lots can be used to identify
501 potential risks to product quality and process controls and to aid the design of a
502 comparability study. If it is not feasible to manufacture full-scale lots for the
503 comparability study, you should perform data-driven risk assessment of CPPs, CQAs
504 (including potency), and other relevant product characteristics to justify that scaling down
505 the manufacturing process provides for an adequate evaluation of the effects of the
506 manufacturing change on product quality.

507

508 A comparability study may be designed as a comparison of historical pre-change testing
509 data to newer data from post-change lots. Such a study design requires that the analytical
510 test methods are equivalent across product lots to provide interpretable data. If analytical
511 methods have changed over time, retained samples from pre-change lots may need to be

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512 reanalyzed using the current analytical methods. You should avoid biased selection of
513 historical data. Ideally, the only differences between the historical pre-change lots and
514 the post-change lots should be the manufacturing changes that are being evaluated in the
515 comparability study. If the pre-change product was manufactured using multiple
516 processes or facilities, comparability should be demonstrated across the pre-change lots
517 before they are included in a comparability study evaluating a newly proposed change.

518
519 For some CGT products, the number of lots may be very small due to, for example,
520 limited manufacturing for rare disease indications, rapid development timelines during
521 clinical studies, or difficulty obtaining cellular starting materials from an adequate
522 number of donors. An insufficient number of lots could compromise statistical power
523 and be insufficient to demonstrate comparability, particularly if there is high lot-to-lot
524 variability, as discussed later in section V.E of this guidance.

525
526 *Special considerations for products derived from a variable cellular starting material*

527
528 Cell-based products where each product lot is derived from a different donor often have
529 product characteristics with very wide ranges due to the inherent variability of the
530 cellular source materials. The number of lots that might be used for such products to
531 perform a statistically valid comparability study could be quite large, or even unfeasible
532 in some cases. However, there are study design considerations that may be useful for
533 decreasing the number of lots included for the comparability study. We recommend that
534 you use a split-source study design, whenever possible. A split-source design limits the
535 impact of cellular variability by splitting individual cellular source materials into two
536 equal portions. One portion of each source material is then subjected to the pre-change
537 manufacturing conditions, and the other portion is subjected to the post-change
538 manufacturing conditions. As described in *Comparability acceptance criteria* later in
539 this section, the results obtained from the split runs should meet the in-process and
540 release specifications and be representative of relevant historical data. Paired difference
541 analysis is typically performed. If a split-source study design is not possible, and it is
542 already known that CQAs for a specific product and clinical indication can vary within a
543 wide range without any adverse impact on product quality, then accordingly, it may be
544 acceptable to set wide acceptance criteria for comparability studies, which would reduce
545 the number of lots for the study.

546
547 When manufacturing cell-based product lots for use in comparability studies, we
548 recommend using the same type of cellular source material that would normally be used
549 to manufacture your product. If this is not feasible due to limited source material or other
550 justified reasons, it may be appropriate to use small-scale manufacturing runs or
551 alternative cellular source material. For example, if patient cells are not available, using
552 cells from healthy donors could be considered. If the number of cells from a single donor
553 is not sufficient to manufacture a large enough lot for the comparability study, it may be
554 possible to use cells pooled from multiple cell collections from the same or multiple
555 donors. In your comparability study report, you should explain why the alternative
556 cellular source material is relevant, including: 1) whether there are differences in process

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557 parameters that might occur when using the alternative material, and 2) whether product
558 quality can effectively be evaluated using the alternative source material. For example,
559 for a product consisting of genetically modified cells, healthy donor cells may not be an
560 appropriate alternative for patient cells, if transduction efficiency is different.
561 Additionally, in the case of product intended to treat a genetic disease, the lack of the
562 genetic defect in healthy donor cells may interfere with measurement of potency.
563

Special consideration for vectors used for ex vivo cell modification

564
565
566 GT vectors⁸ used for ex vivo cell modification must be manufactured in compliance with
567 current good manufacturing practices (cGMP) under section 501(a)(2)(B) of the Federal
568 Food, Drug, and Cosmetic Act (FD&C Act), as appropriate for the stage of development
569 (Ref. 11). This should include effective quality risk management and change control
570 activities (Ref. 1). Changes to the manufacturing of GT vectors should be carefully
571 evaluated not only for risks to the quality of the vector and the performance of the vector
572 manufacturing process, but also for risks to the quality and manufacturing process
573 performance for the ex vivo gene-modified cells.
574

575 Analytical comparability of the vector should typically be evaluated using the vector
576 release assays (including an assay that measures the biological activity of the vector), as
577 well as any relevant characterization assays, if appropriate. In addition, the effect of the
578 vector manufacturing change on the quality of the ex vivo gene-modified cells (DS
579 and/or DP) should be evaluated in an analytical comparability study using an adequate
580 number of vector, DS and/or DP lots.
581

582 The number of vector lots available for comparability studies may be small in situations
583 where each lot of vector is sufficient for the manufacture of large numbers of DP lots. In
584 such cases, it may be appropriate for comparability studies to include vector lots that
585 were manufactured during process development or engineering runs, if manufacture of
586 these vector lots is similar to the manufacture of the vector lots used to manufacture DP
587 for clinical studies. Your risk management strategy should ensure that sufficient vector
588 lots will be available for future comparability studies because difficulties in
589 implementing vector manufacturing changes can cause delays in clinical studies or
590 shortages in licensed products.
591

Assessment of potency

592
593
594 The biological activity of CGT products can be highly sensitive to manufacturing
595 changes. Therefore, we recommend that a quantitative potency assay (Ref. 12) be
596 included when performing analytical comparability studies. You may wish to consider
597 using several analytical methods to evaluate potency if the routinely used analytical

⁸ For the purposes of this guidance, a “vector” is defined as a vehicle consisting of, or derived from, biological material that is designed to deliver genetic material. Examples include plasmids, viruses, and bacteria that have been modified to transfer genetic material. (Long Term Follow-Up After Administration of Human Gene Therapy Products; Guidance for Industry; January 2020, at 29, available at <https://www.fda.gov/media/113768/download>).

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598 method is imprecise or unable to assess all aspects of the product’s MOA that might be
599 affected by the manufacturing change. For some products, animal models may be used to
600 supplement a relevant quantitative assay(s) to demonstrate that the product has the
601 desired biological effect and to provide supportive evidence for comparable biological
602 activity of the pre-change and post-change product.

603
604 CGT products may have multifaceted mechanisms of action due to, for example, product
605 complexity, the presence of multiple active ingredients, and complex PK/PD profiles.
606 Assays that measure relevant biological activities of CGT products are challenging to
607 develop, and these assays are often inherently variable. These difficulties can delay
608 establishing a potency assay and release acceptance criteria until later-stage clinical
609 studies because the relationship between the product’s MOA and safety and effectiveness
610 may not be well understood. Yet, exclusion of potency analysis from a comparability
611 evaluation compromises the conclusions drawn from a comparability study. To avoid
612 this situation, we recommend that samples be retained from all lots to facilitate future
613 analysis of potency to support comparability.

614
615 When establishing an acceptance criterion for potency in comparability studies, you
616 should consider that product quality may be adversely affected not only by a significant
617 decrease in potency, but also if there is a significant increase in potency. A
618 manufacturing change that significantly increases potency, even if intentional, may raise
619 safety concerns. In such cases, if you are unable to demonstrate that the change will not
620 adversely affect safety, the post-change product will not be considered comparable to the
621 pre-change product.

Comparability acceptance criteria

622
623
624
625 It is not necessary for the measurements of pre- and post-change CQAs to be identical to
626 reach a conclusion of comparability if there is evidence demonstrating that there is no
627 adverse impact of the change on product quality. A comparability acceptance criterion
628 should be defined prior to initiating the comparability study for each CQA determined,
629 through risk assessment, to have a potential to be impacted by the change. For
630 quantitative attributes, a comparability acceptance criterion may be defined as the largest
631 acceptable difference between the pre-change and post-change attribute (an equivalence
632 margin) or as an acceptable range for the post-change attribute (a quality range). In
633 addition to meeting the comparability acceptance criteria, lots used in comparability
634 studies should also meet the established in-process and release acceptance criteria, and,
635 unless otherwise justified, the results should be representative of data (e.g., mean,
636 standard deviations, median) from relevant pre-change historical lots.

637
638 An equivalence approach is often appropriate for evaluating comparability of CQAs
639 when it is important to directly compare the pre- and post-change values and determine
640 whether they are sufficiently similar. For normally distributed data, the equivalence
641 margin should be defined as the maximum acceptable difference in population means.

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642 Exceeding this margin would be interpreted as an adverse effect of the post-change
643 manufacturing process on product quality.

644
645 A quality range approach evaluates whether the post-change quality results fall within a
646 defined range. This range should often be narrower than the release acceptance criteria
647 for those same quality attributes. The quality range approach can potentially be used for
648 attributes with various risk levels, but higher-risk attributes should be evaluated using the
649 more rigorous equivalence approach. The number of post-change lots sufficient for a
650 comparability study when using the quality range approach will depend on the totality of
651 evidence supporting the lack of adverse effect of the change on product quality. For
652 example, if additional relevant data from other studies (such as impurity clearance studies
653 or other process characterization studies) provide evidence that the manufacturing change
654 does not have an adverse effect on a particular quality attribute, then this may justify the
655 use of a smaller number of post-change lots in the comparability study. Otherwise, you
656 should ensure that the comparability study is designed with sufficient power by
657 calculating the number of post-change lots needed to demonstrate with high confidence
658 that an appropriate proportion of future lots will fall within the quality range.

659
660 Regardless of the approach used, comparability acceptance criteria should ideally be
661 based on understanding the potential effect of the attribute on the safety and effectiveness
662 of the product, and not based solely on statistical analysis of historical data from the pre-
663 change product. If there is clinical or manufacturing experience supporting the
664 differences in CQAs that negatively and/or positively impact product quality, you should
665 use this information to select appropriate quality ranges or equivalence margins for your
666 comparability study. If instead you are using statistical analysis of historical data to
667 define comparability acceptance criteria (e.g., based on standard deviation), you should
668 justify how your statistical-based acceptance criteria are adequate to ensure the safety and
669 effectiveness of the post-change product (i.e., justify how your statistical-based parameter
670 is relevant to a biologically meaningful difference).

671
672 Please refer to section V.E of this guidance regarding statistical analysis of comparability
673 study results.

674 **C. Analytical Methods**

675
676 Interpretation of comparability test results depends on the suitability of the analytical
677 methods used. For example, using an imprecise, insensitive, or inconsistent method in a
678 comparability study can invalidate the conclusions of the study. We recommend that you
679 provide a tabular listing of the analytical methods and testing sites used in the
680 comparability study. If method descriptions, qualification studies, or validation studies
681 are provided elsewhere in your application, you may refer to them. For comparability
682 studies of investigational products, all release assays used to demonstrate comparability
683 should be qualified or validated, depending on the phase of clinical study. Assays used
684 for extended characterization do not necessarily need to be qualified, but they should be
685 scientifically sound and fit for their intended use, be sufficiently precise to detect
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687 meaningful differences in product quality, and provide results that are reliable. If not
688 described elsewhere, you should describe sample acquisition (e.g., process step, sample
689 volume, storage temperature) and justify any differences in acquiring samples from the
690 pre-change and post-change manufacturing processes.

691
692 FDA has issued guidance providing general guiding principles to assist applicants with
693 assay validation (Refs. 13, 14). Some of the challenges with validation of assays for CGT
694 products are highlighted below:

695 696 *Analytical Method Precision*

697
698 Small changes in an attribute can sometimes have a profound impact on the quality of
699 CGT products. However, measuring such small changes can be challenging when the
700 analytical methods are not precise. Therefore, it is especially important that the
701 analytical methods used to assess the effect of manufacturing changes on product quality
702 and process control are sufficiently precise. For example, if a 5% change in a particular
703 cell marker represents a meaningful difference in product quality, then a flow cytometry
704 assay with an intermediate precision of 20% coefficient of variation would not be
705 adequate for evaluating whether there is a meaningful difference in that attribute between
706 the pre-change and post-change products.

707 708 *Consistent Method Performance*

709
710 Analytical methods are often changed, added, or transferred to a new facility over the
711 course of a CGT product lifecycle because of advancing technology and/or increasing
712 understanding of MOA. To provide the most readily interpretable data for a
713 comparability study, we recommend that you perform side-by-side testing⁹ of pre-change
714 and post-change product attributes or analyze all samples using the same analytical
715 method performed at the same testing facility. Reference material should also be used, if
716 available.

717
718 At all stages of the product lifecycle, when changing an assay or transferring an assay to
719 a new testing facility, you should perform a risk assessment for the assay change to
720 determine if there is a potential impact on evaluation of product quality, including
721 evaluations conducted in comparability studies. For example, a change to an ELISA kit
722 from a manual to an automated method could result in meaningful differences in
723 sensitivity or precision. The equivalence of the old and new assays should be evaluated
724 by testing identical samples with each assay. Similarly, when using multiple facilities to
725 perform the same assay, a method transfer study should be performed to ensure
726 reproducibility, and the assays should include identical samples or common reference
727 materials to ensure consistent assay readouts. Additional assay qualification or validation
728 may also be warranted after transferring an assay to a new facility (Ref. 13).

⁹ In this guidance, side-by-side testing, also often referred to as “head-to-head” testing, means testing of the pre- and post-change samples in the same experiment.

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D. Results

For each product attribute and process parameter assessed, we recommend that the results for each lot and the corresponding lot numbers be provided in a tabular format, together with tables that list summary statistics for the data alongside the predefined study acceptance criteria. When appropriate, we recommend that you also display data in a graphical format. We recommend that you describe and analyze any differences in the study data between the pre-change and post-change products. Any deviations from pre-established procedures should be described and justified.

E. Statistics

When designing comparability studies for CGT products, appropriate statistical methods should be used to determine if the pre- and post-change products are comparable. The statistical methods should be defined in the comparability protocol before executing the comparability study. Selection of a statistical approach to demonstrate comparability of pre- and post-change products can be challenging when there are only a limited number of samples, when quality attributes are highly variable, or when the data is not normally distributed.

We recommend that you consult with a statistician before discussing the study design and statistical approach with FDA. In general, there could be multiple appropriate statistical methods that may be used to evaluate whether data from the post-change product are within predetermined acceptable limits. To avoid errors in the design and analysis of comparability studies, a careful consideration of fundamental statistical concepts is important. For example:

- Some statistical methods may be inappropriate for a given comparison due to invalid assumptions, a need for a very large number of samples, high variability in sample data, or limited information about the population distribution. For example, parametric tests that assume a normal population distribution should not be used if the data are not normally distributed. When justified, data transformation could be useful to meet the assumption of data normality. You should describe the statistical method, justify the assumptions of the statistical approach, justify the acceptance criteria selected, and discuss limitations. Different statistical methods may be used within the same study to analyze different CQAs, if the CQAs differ in their underlying distribution (e.g., normal vs. binomial).
- The variability of a statistic is determined by the spread of its sampling distribution. Having only a small number of lots can lead to greater sampling variability, which can significantly reduce the statistical power. Therefore, the appropriate number of lots should be considered early, as the lack of sufficient numbers of samples may impede comparability analysis and implementation of

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- 774 manufacturing changes, especially during late-stage development and after
775 licensure.
776
- 777 • As described in section V.C of this guidance, it can be difficult to evaluate the
778 comparability of an attribute when using an assay that has poor precision. In such
779 situations, an alternative to improving the precision of the assay would be to
780 reduce measurement uncertainty by performing the assay multiple times
781 independently for each lot and reporting the mean value. Such an approach will
782 improve the statistical power of the comparability analysis for that attribute. It is
783 important to note that the mean of the assay results for each lot should be treated
784 as a single data point when analyzing comparability; it is inappropriate to treat
785 each individual assay result as an independent data point in the comparability
786 analysis.
787
 - 788 • For studies that compare two cellular manufacturing processes using split-donor
789 starting material, the product data from each donor are paired. In such cases, you
790 should select a statistical test suitable for analysis of the difference between paired
791 data, rather than a test that assumes an independent data structure.
 - 792 • The absence of a statistically significant difference between the pre- and post-
793 change products (e.g., $p\text{-value} > 0.05$) does not demonstrate comparability. For
794 example, using a two-sample t-test is not appropriate for comparability claims
795 when the null hypothesis is that the means of CQAs of pre- and post-change
796 products are equal, and the alternative hypothesis is that they are different. In
797 other words, failing to reject this null hypothesis is not the same as showing
798 equivalence.
799
 - 800 • To evaluate equivalence, you may consider calculating an appropriate confidence
801 interval for the difference between the pre- and post-change data, and conclude
802 equivalence if this confidence interval is within the equivalence margin. When
803 the CQA of interest is a mean value, you may consider using the ‘Two-One-Sided
804 Tests procedure’ (TOST) or other appropriate statistical method to establish
805 comparability. For some attributes (e.g., impurity, viability), it may be possible to
806 demonstrate that the manufacturing change has no adverse effect on product
807 quality using a one-sided statistical comparison, such as non-inferiority testing or
808 other appropriate method.
809
 - 810 • If the lots selected for the comparability study are not representative of your
811 typical manufacturing process, the corresponding results will have limited
812 meaningful interpretation, regardless of the particular statistical methodology
813 applied. You should justify your selection of comparability lots and (if
814 applicable) the cellular source material used to produce those lots.
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816 **VI. SPECIAL CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL** 817 **PRODUCTS**

818
819 Tissue-engineered medical products (TEMPs)¹⁰ commonly incorporate viable cells and
820 scaffolds, with cells either seeded onto the scaffold's surface or embedded within the scaffold.
821 Oftentimes, TEMPs are intended to mimic the in vivo cellular microenvironment. Although
822 manufacturers are gaining experience with these products, there is generally still limited
823 understanding regarding product quality, interactions between the cells and scaffolds in vitro
824 (e.g., maturation), interactions of the DP with the host environment (e.g., remodeling), and
825 sensitivity of TEMPs to manufacturing changes. For these reasons, manufacturing changes to
826 TEMPs pose additional unique challenges, as changes may impact the cells, the scaffold and/or
827 the combined cell-scaffold product in ways that are not readily anticipated or detectable based on
828 current measurement technologies.

829
830 We recommend that you conduct a thorough risk assessment that considers the potential effects
831 of the change on each component (e.g., cells, scaffold) and on the final cell-scaffold construct.
832 The risk assessment should determine whether a comparability study is necessary to evaluate any
833 potential impact of the change on product quality and whether this comparability study should
834 evaluate the cells, scaffold, cell-scaffold intermediate(s), and/or the cell-scaffold DP.

835
836 When assessing manufacturing changes to TEMPs, you should consider scaffold characteristics,
837 including but not limited to the scaffold source (e.g., natural or synthetic), density, shape,
838 mechanical and physicochemical properties, interactions with cytokines and growth factors, and
839 capacity for inducing cell signaling pathways (e.g., via mechanotransduction). Similarly, you
840 should consider relevant cell characteristics, including but not limited to cell morphology,
841 density, aggregation, growth, viability, and the relevant biological function(s) for the proposed
842 specific indication. Both manufacturing changes introduced before combining the cells and
843 scaffold and manufacturing changes introduced after combining the cells and scaffold (e.g.,
844 changes to the culture conditions, packaging, storage or shipping) may have a significant impact
845 on the overall biological activity and/or performance of the TEMP. Therefore, comparability
846 studies for TEMPs should often include evaluation of the effect on DP quality even when
847 manufacturing changes are made only to the scaffold or to the cells prior to combining these two
848 components.

849
850 Furthermore, certain changes may have a significant impact on how the DP behaves after
851 administration in terms of safety and performance, and therefore on product quality. You
852 should, therefore, assess the potential impact of the change on product quality
853 post-administration (e.g., remodeling, degradation). Depending on the outcome of the risk
854 assessment, you may need to evaluate the performance of the TEMP in a physiologically
855 relevant environment to demonstrate comparability. This may involve additional nonclinical
856 studies and/or clinical studies.

857

¹⁰ For the purposes of this guidance, TEMPs are limited to products that consist of living cells combined with a scaffold or substrate regulated under section 351 of the PHS Act.

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858 In general, the need to maintain the integrity and structure of TEMP_s may make it difficult to
859 acquire samples for testing and retention. In addition, products that are manufactured in a closed
860 system, such as a bioreactor, could pose additional practical challenges to acquiring samples.
861 Further, the seeding and growth of cells on the scaffold may not be uniform, making it difficult
862 to obtain representative samples. Therefore, it is important to consider these unique challenges
863 in the context of comparability study design, if relevant, surrogate¹¹ TEMP_s could be
864 manufactured in parallel during clinical lot production or manufactured during specific
865 production for a comparability study. Such surrogate TEMP_s could be particularly useful when
866 destructive sampling is used for testing additional CQAs that are not routinely evaluated for lot
867 release. An alternate approach could include sampling of the incubation media instead of the
868 product itself, when the incubation media can be considered a representative sample of the
869 product for the specific CQAs.

870

871

872 **VII. COMMUNICATION WITH FDA**

873

874 We recommend that sponsors and applicants of CGT products prospectively discuss proposed
875 significant manufacturing changes with FDA’s Center for Biologics Evaluation and Research
876 (CBER), particularly when such manufacturing changes would be implemented during later
877 stages of the product lifecycle. Communication with the FDA can be sought either by requesting
878 FDA comment on relevant information submitted in an IND amendment or BLA product
879 correspondence, or through a formal meeting request (Ref. 15). The type of meeting used for
880 such discussions depends on the stage of the product lifecycle and the issues to be considered.

881

882

¹¹ For the purposes of this guidance, “surrogate” refers to an additional unit of the drug product that is manufactured in parallel to the clinical product for characterization purposes, which may include destructive testing.

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

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