November 13, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-D-2436 for Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products

Dear Sir/Madam:

The Alliance for Regenerative Medicine ("ARM") is pleased to submit comments to the U.S. Food and Drug Administration ("FDA" or "the Agency") in response to the recently released draft guidance titled, *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products* ("Draft Guidance").

ARM is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 400 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

ARM applauds the FDA for issuing this Draft Guidance and appreciates the effort and attention that the Agency devoted to drafting comprehensive recommendations and guidelines that take into consideration the unique challenges that developers of cellular and gene therapy (CGT) products face when managing manufacturing changes for investigational and licensed products. Below we provide high-level feedback regarding certain themes that emerged from our membership's consideration of these guidelines. A more detailed line-by-line analysis is provided in the table in the next section. Although our comments point out where certain recommendations may not be well-suited for gene or cell therapy products or where additional clarity would be helpful for CGT developers, we wish to underscore that the Agency's

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commentary in the Draft Guidance is generally in line with our members' experiences, and we hope that our input will be useful to the Agency as it works towards finalizing the guidance.

One overarching comment is that the Draft Guidance largely provides recommendations regarding major changes to manufacturing when the product and manufacturing process are well-understood (e.g., references to CPPs, CQAs, quantitative potency assays). We find this inconsistent with the overall message that major changes should not be made late in development, because the comparability strategy that the guidance contemplates requires robust process knowledge that manufacturers typically only gain at later stages in development. ARM recognizes that sponsors need to understand as much as possible about potential critical quality attributes (CQAs) early, especially for programs with expedited clinical designations, to allow a change to a commercial process before obtaining all clinical data. However, at an early stage of development (i.e., through first-in-human (FIH) trials), sponsors might not yet have well-defined CQAs and/or critical process parameters (CPPs). Furthermore, during early-stage development, links between CPPs and CQAs may not be well-established, which makes the proposed risk assessment approach harder to implement. Therefore, we suggest that the Agency provide more clarification on which recommendations apply to products in FIH studies versus products that are in later stages of development (e.g., pivotal, post approval), allowing for greater accommodation for limitations in product knowledge and manufacturing experiences early in product development.
ARM requests the Agency to discuss the implications for including non-critical attributes in the comparability study and the need to establish acceptance criteria for quality attributes that have been determined not to be critical.

Another general observation is that the Draft Guidance does not differentiate its expectations or recommendations based on cell and gene therapy product classes. There are, however, significant differences in the level of product understanding and characterization between CGT product classes. For example, viral vectors are less complex and better characterized than cell therapy products, so many of the assumptions that the document makes regarding a lack of product understanding are not accurate for viral vector manufacturing and development. Viral vectors, in many ways, more closely resemble protein therapeutics than cell therapies in terms of raw materials, manufacturing processes, level of product characterization, and control strategies.

We also note that, for certain recommendations, the Draft Guidance does not describe a phase-appropriate approach to performing comparability studies. There are also some apparent inconsistencies in the Draft Guidance with respect to risk assessments that may require further clarification. The Draft Guidance essentially discourages any manufacturing changes after the early development phase but suggests that waiting for real-time stability data may severely delay the ability to implement manufacturing changes. This position does not recognize that for many CGT products, changes can be effectively risk assessed and evaluated via analytical assessment to verify that the product's safety, efficacy, and stability profiles have not been

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adversely affected. This position also does not take into account advances in platform technology, the development trajectory of rare diseases, or timelines associated with accelerated programs, and may limit the industry's ability to implement process changes needed to ensure commercial supply such as manufacturing scale-up or site change.

The Draft Guidance acknowledges that there are often limitations on the number of lots available to assess product changes, but then advises using statistical approaches that require larger numbers of lots to achieve appropriate levels of statistical power that are meaningful to indicate comparability, which may not be feasible for rare disease indications with low numbers of lots. The Draft Guidance provides brief recommendations specific to *ex vivo* viral vectors for how to approach situations when the number of lots is limited, but this needs to be expanded and applied to other product classes as well. ARM suggests that the guidance include a discussion of scenarios where the use of descriptive statistics would be reasonable. In addition, in some cases a product may show statistical differences pre- and post-change, but may still be considered to be comparable if the differences can be justified. ARM requests the agency to discuss the considerations/justification that may allow a determination of comparable despite not meeting pre-defined statistical criteria.

While the Draft Guidance seeks to cover a diverse product mix, the Agency should give further consideration to the fact that the type and phase of change made carries a different level of risk across product types. For example, a manufacturing site change for a platform adeno-associated virus (AAV) during a phase 3 study might carry less risk than a similar change for a novel cell therapy. We recommend that FDA provide product-type risk discussions in each section or, alternatively, a standalone section that discusses risk-based expectations across product types.

Manufacturing changes and any ensuing comparability studies can be a key enabler in the development of CGT products, with implications across non-clinical, clinical and CMC disciplines. While we are encouraged to see sections of this Draft Guidance specifically call out potential implications for clinical studies, we encourage the Agency to continue to address this topic holistically and not as an isolated procedure for making and communicating manufacturing changes. ARM suggests that the Agency revise the Draft Guidance to clarify IND amendment documentation requirements.

We also request that the Agency specifically define what is considered a change in "the production process" and what is a change in "quality controls" in the context of this guidance. ARM recommends that the guidelines acknowledge that not all manufacturing changes will result in the creation of a new product.

Throughout the document, FDA emphasizes that sponsors need to demonstrate that a manufacturing change will not result in any adverse impacts on product quality, safety, or efficacy, but the recommendations provided may overestimate the current understanding and

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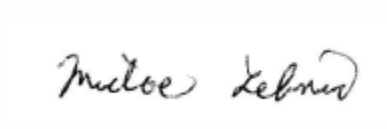
abilities in the field to predict and demonstrate the impact of planned manufacturing changes. We also recommend that the Agency clarify whenever the phrase "…ensure that the change does not adversely impact product quality" is used that the Agency clarify whether the phrase refers only to negative impacts to product quality or if it also refers to improvements to product quality.

The guidance provides an emphasis on clinical studies in the absence of adequate analytical comparability data, or where variability is seen which may be inherent to some types of CGT products. For some types of CGT products, clinical studies may be complex / not straight-forward. Thus, it would be helpful for the guidance to provide more specific direction regarding the expectations for such studies.

We recommend that FDA elaborate on how to identify or assess how improved product quality could lead to "a significant benefit in effectiveness and/or safety" that would result in a different product such that safety and efficacy data from the pre-change product cannot be leveraged/pooled and what next steps a sponsor should take if such a benefit is discovered. The guidance should also have a section that describes differences in product that require a different IND versus differences in product that do not support leveraging/pooling safety and/or efficacy data from the pre-change product (while allowing further product development under the same IND). The Draft Guidance could benefit from a hypothetical case study on how comparability should be assessed when a post-change product is expected to improve in a product safety-related attribute and is therefore not analytically comparable to the pre-change product.

Sincerely,



Michael Lehmicke
Senior Vice President, Science and Industry Affairs

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Specific Line-by Line Comments

Text in brackets are proposed additions and strikethrough text are proposed deletions.

Section & Line Numbers	Guidance text	Comment and, Where Applicable, Rationale for Proposed Change	Proposed Change
I. Introduction			
17-21	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.	The guidance document should clearly delineate that demonstrating comparability during the IND stage is decidedly different than demonstrating comparability post-BLA approval. The proposed addition provides a needed distinction in phase appropriate standards between demonstrating comparability during IND stages or post BLA approval.	"…with recommendations regarding **[pre- and post-approval]** product comparability and the management of manufacturing changes for **[both]** investigational and licensed CGT products."
II. Background			

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35-40	CGT products are regulated under the existing framework for biological products. Manufacturing and control of CGT products can often be affected by unique factors, including limited knowledge of product quality attributes, limited manufacturing experience, limited and variable starting materials, limited amount of product, complex manufacturing processes, and limit-ed product shelf life. These aspects of CGT products may make the management of manufacturing changes more challenging than for other biological products.	• The use of "may" is too non-committal. These aspects of CGT products are clearly believed to make management of manufacturing changes more challenging. Suggest substituting another word such as "generally."	"…These aspects of CGT products ~~may~~ **[generally]** make the management of manufacturing changes more challenging than for other biological products (i.e., monoclonal antibodies, recombinant therapeutic proteins)."
44-49	We note that while improvement of product quality is always desirable and encouraged, if the results of comparability studies indicate an improved product quality suggesting a significant benefit in effectiveness and/or safety, the pre- and post-change products may be different products and, therefore, not comparable.	• In the first sentence (line 46-47), improved product quality and impact of such an improvement is discussed, however the proposed risk assessment described in line 52-53, suggests only risks with potential to adversely affect the product quality are considered. The wording is ambiguous and counterintuitive as the risk assessment would not highlight risk of significant product improvement. Therefore, the risk assessment should be able to	We note that while improvement of product quality is always desirable and encouraged, if the results of comparability studies indicate an improved product quality suggesting a significant ~~benefit~~ **[change]** in effectiveness and/or safety, the pre- and post-change products may be different products **[with different product CQAs]** and, therefore, not **[analytically]** comparable **[for all attributes]**.

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		identify *any* change to product quality. • If, for example, empty capsid is lowered resulting in improved safety that would potentially make it a different product. The word "change" would be more suitable than "benefit." • The guidance document should define or at least elaborate on the term "different products." If a different product means that a different IND is needed or a new clinical study is needed, then this would discourage sponsors from improving product quality. • If a risk assessment indicates that a manufacturing change has the potential to affect product quality, comparability studies should be performed.	
52-54	If a risk assessment indicates that a manufacturing change has the potential to adversely affect product quality, comparability studies should be performed to evaluate the impact of the proposed manufacturing change.	• The use of the word "adversely" contradicts the last sentence of the previous paragraph (lines 46-49), which states that post-change product with improved product quality may be different products and therefore not comparable.	

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		• The document is not consistent with regards to improved product quality and comparability. • We suggest that the Agency carefully choose between "risk assessment" and "impact assessment" since they have different connotations that will lead to different interpretations.	
54-57	It can be difficult to fully characterize CGT products using analytical methods, and in some cases analytical studies alone may not be sufficient to reach a conclusion regarding comparability. In such cases, additional data from nonclinical studies may help to support comparability.	• This is a very broad statement compared to the position reflected in the ICH Q5E guidance document. There is limited discussion in this document about factors or situations that would indicate that nonclinical or clinical data are required. Additional guidance similar to that outlined in ICH Q5E Section I.D (1.4) should apply, i.e., quality attributes are compared, risk to safety and efficacy is assessed, and the need for a targeted nonclinical or clinical study is determined based on the risk assessment. • Could the Agency provide examples where nonclinical studies would be supportive in addition to analytical comparability?	It can be difficult to fully characterize CGT products using analytical methods, and in some cases analytical studies alone may not be sufficient to reach a conclusion regarding comparability. ~~In such cases, additional data from nonclinical studies may help to support comparability.~~

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57-58	Otherwise, additional clinical studies may be warranted.	Please clarify wording.	~~Otherwise, additional clinical studies~~ **[If the analytical and nonclinical studies are inconclusive]**, additional clinical studies may be warranted.
60-63	The extent of analytical evaluation needed to adequately evaluate a manufacturing change in comparability studies generally increases with the stage of clinical and product development and should be supported by knowledge of critical quality attributes (CQAs) (Ref. 3), accumulated manufacturing experience, and further understanding of the mechanism of action (MOA).	Clear identification and understanding of the MOA for a tissue engineered construct can be a troublesome challenge. We request recommendations about how to address this issue in the context of demonstrating comparability for pre- and post-manufacturing change(s) in the context of a limited understanding of MOA.	
69-71	Applicants must also demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies that each manufacturing change does not adversely affect product quality before distributing a product manufactured using the change (21 CFR 601.12(a)(2)).	• The text in the guidance states that validation is required to support manufacturing changes in this situation. It is not clear if there are other alternative approaches to demonstrate that the process remains in control, e.g., use of Continued Process Verification (CPV) data to support that minor changes do not impact the state of control.	Applicants must also demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies that each manufacturing change does not adversely affect product quality before distributing a product manufactured using the change (21 CFR 601.12(a)(2)). **[In lieu of additional validation, alternative approaches may be acceptable, e.g., use of Continued Process Verification (CPV) data to support that minor changes do not impact the state of control.]**

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74-75	For investigational products, sponsors must provide sufficient chemistry, manufacturing, and control (CMC) information to assure product safety, identity, quality, purity, and strength (including potency) of the product (21 CFR 312.23(a)(7)(i)), and some manufacturing changes without adequate comparability data may result in a clinical hold (21 CFR 312.42(b)).	Suggest rewording.	For investigational products, sponsors must provide sufficient chemistry, manufacturing, and control (CMC) information to assure product safety, identity, quality, purity, and strength (including potency) of the product (21 CFR 312.23(a)(7)(i)),"and some manufacturing changes ~~without adequate comparability data may result in a clinical hold (21 CFR 312.42 (b))~~ **[may require additional *in vivo* data to ensure absence of adverse effect on product quality].**"
77-90	The guidance entitled "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" dated April 1996 (Ref. 4) contains general recommendations applicable to biological products, but it does not address the specific challenges of performing comparability studies with CGT products. The guidance entitled "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" dated June 2005 (Ref. 5) contains principles that may be useful for comparability studies of CGT products. However, its scope is limited to certain proteins and polypeptides that can be	• Neither the 1996 guidance "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products" nor the 2005 guidance titled "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process" reference statistical approaches to be relied upon for demonstration of comparability. • The glossary in the 2005 guidance "Q5E Comparability of Biotechnological/Biological Products Subject to Changes in	

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	highly purified and characterized, which are typically less complex, better characterized, and manufactured to more stringent tolerances than CGT products. Other FDA guidance documents related to management of manufacturing changes and risk management for biological products generally do not address specific CGT product challenges (e.g., Refs. 1, 2, 6). The purpose of this guidance is to provide recommendations for managing manufacturing changes and assessing comparability for both investigational and licensed human CGT products while considering the unique challenges that apply to these products.	Their Manufacturing Process" defines "comparable" as: "A conclusion that products have **highly similar** quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion." ARM suggests the concept of "highly similar" quality attributes be added to this DRAFT Guidance. • Will this new guidance supersede previous guidance with respect to comparability demonstration for cellular and gene therapy products?	
		Many viral vectors are highly purified and characterized biologics using manufacturing processes and analytical methods that are very similar to those used for protein therapeutics. Production, control and characterization of *in vivo* viral vectors such as AAV are much more similar to therapeutic proteins than other CGT product classes such as cell therapies.	

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		Because viral vectors have more similarities to protein therapeutics than cell therapies, it may be more appropriate for viral vectors to fall under the ICH Q5E guidelines. The guidance should be updated to clarify which, if any, of the recommendations apply to viral vectors and explain whether manufacturing for viral vectors should follow ICH Q5E or other guidelines.	
		Lines 83-85: Internationally recognized guidance still provides agreed upon framework for comparability assessment of biotechnology products. Some CGT products can be well characterized and as technology progresses, the ability to characterize will likely improve. Moreover, the phrase "*and manufactured to more stringent tolerances than CGT products*" is not applicable to all CGTs and has a negative connotation because it implies that less stringent tolerances or standards are employed in the manufacture of CGTs.	However, its scope is limited to certain proteins and polypeptides that can be highly purified and characterized, which are typically less complex~~,~~ **[and]** better characterized.~~, and manufactured to more stringent tolerances than CGT products.~~
III. Considerations for the Management of Manufacturing Changes			
96-99	An effective quality system maintains consistency in drug product (DP) quality throughout the product lifecycle, including by adequately managing manufacturing	• We recommend including a reference to 21 CFR § 210, as change control procedures	

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	changes. In general, manufacturing changes should be thoroughly assessed and documented using effective change control procedures.	requirements vary between Phase 1 and later phase development. • Please clarify from which point onwards should changes be captured using change control procedures. Can this be documented in a report for early-stage programs, rather than with a quality event?	
99-101 [some comments and changes requested apply throughout the document]	For investigational products, maintaining product quality by control of CQAs and critical process parameters (CPPs) during manufacturing changes is important for obtaining interpretable clinical study data that can support licensure.	• Because CQAs and CPPs are typically not well understood at early phases of development, a phase-appropriate approach for investigational products should be acknowledged in the discussion. See, for example, points outlined in "Chemistry Manufacturing and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)", Section IV.A. Depending on the phase of development, the criticality of attributes and / or parameters might not be established. ○ "Your summary should also include a description of potential CQAs that are relevant to the safety and biological activity of the product as they are understood at the time of	For investigational products, maintaining product quality **[is important for ensuring consistent product dosed in clinical trials designed to demonstrate safety and efficacy.]** ~~by control of CQAs and critical process parameters (CPPs)~~ **[Controlling relevant quality attributes and process parameters]** during manufacturing changes is important for **[ensuring consistent product dosed in clinical trials designed to demonstrate safety and efficacy and]** obtaining interpretable clinical study data that can support licensure. **[The extent that CQAs and critical process parameters (CPPs) can be used to support manufacturing changes will depend on the stage of clinical and product development**

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		submission.... We acknowledge that limits may be broader during early development when you are still gaining information about your product. In addition, as your product progresses through development the list of potential CQAs may be revised as your knowledge of the product increases. " ○ "We recommend that you monitor process performance parameters for process consistency. Process trend analysis and evaluation of process parameters and materials will help to determine and establish process control strategies. "	**and the sponsor's current knowledge about the product and experience with manufacturing. Sponsors are encouraged to use a robust Quality by Design approach from early in development.]**
101-103	"A robust framework for managing manufacturing changes is especially valuable for CGT products because of the complexity of these products and their manufacturing processes."	A robust framework for managing manufacturing changes is a component of GMPs and is expected for all drug products, not just for CGT.	We propose deleting this sentence.
A. Risk management			

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112	Q9 Quality Risk Management (Ref. 1)	• Q9(R1) was published in May, 2023	
114-116	Defining acceptable ranges for CQAs and establishing operating ranges for CPPs prior to making a manufacturing change facilitates conducting a risk assessment and evaluating the change.	To achieve yield, scale, quality or other improvements, a process may be required to extensively overhaul unit operations. Please clarify 1) that additional characterization can be sufficient if unit operations are not identical, or 2) that process improvement can be used to justify unit operations that differ between processes if they are nevertheless equivalent (comparable) based on their analytical outputs.	**[Sponsors should understand the impacts of process parameters and process inputs on product quality attributes]** prior to making a manufacturing change [**to**] facilitate~~s~~ conducting a risk assessment and evaluat**ing** the change. **[As the product progresses through development, sponsors should]** defin**e** acceptable ranges for CQAs and establish~~ing~~ operating ranges for CPPs **[and acceptable quality for critical raw materials, when possible.]**
126-129	Additionally, introducing a manufacturing change at this late stage of development or after licensure could require additional process performance qualification studies if the existing qualification study is not representative of the intended commercial process (e.g., 21 CFR 211.22, 211.100, 211.110(a) and 211.165).	• Please clarify how to assess or establish whether the existing qualification study is representative of the intended commercial process. • It is unclear how the CFR references in parenthesis are relevant to this assessment: ○ 21 CFR 211.22: Responsibilities of quality control unit.	

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		○ 21 CFR 211.100: Written procedures; deviations. ○ 21 CFR 211.110(a): Sampling and testing of in-process materials and drug products. ○ 21 CFR 211.165: Testing and release for distribution.	
120-141	Factors such as product and process knowledge, qualification/validation of methods, and the stage of clinical development should be considered when assessing the risk of the manufacturing change. In particular, you should carefully assess risks to product quality if extensive manufacturing changes are introduced shortly before BLA submission. In such a situation, a comparability study should be comprehensive and should provide high confidence that the change does not adversely impact product quality (section V of this guidance). Additionally, introducing a manufacturing change at this late stage of development or after licensure could require additional process performance qualification studies if the existing qualification study is not representative of the intended commercial process (e.g., 21 CFR 211.22, 211.100, 211.110(a) and 211.165). For a process that has already been validated, you should also determine	• The acceptability of using platform approaches or platform data from similar products should be introduced as a way to mitigate risk of a change or a way to use prior knowledge when designing a manufacturing process that will undergo changes prior to licensure. For example, platform data could be included as a potential source of supporting information for risk assessment (e.g., impurities from a different product using the same manufacturing process and route of administration). • Lines 132-138: "Extensive manufacturing changes" should be defined, with examples. It may not be possible to make all "major" manufacturing changes prior to phase 3, especially for programs working on accelerated timelines	Lines 122-123 In particular, you should carefully assess risks to product quality ~~if extensive manufacturing changes are introduced shortly before BLA submission~~ **[for changes introduced during clinical development that are determined, based on the risk assessment, to be high risk.]** Lines 126-127 Additionally, introducing a manufacturing change ~~at this late stage of development~~ **[during the late stages of development] or after licensure could require additional process performance** qualification studies if the existing qualification study is not representative of the intended commercial process (e.g., 21 CFR

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	whether there is a need for any changes to the plans for continued process verification as a result of the manufacturing change (Ref. 7). For these reasons, we recommend that any extensive manufacturing changes be introduced prior to initiating clinical studies that are intended to provide evidence of safety and effectiveness in support of a BLA. To facilitate manufacturing changes during rapid clinical development, CGT product manufacturers should ensure that the pace of product development is aligned with the stage of clinical development. For example, if you initiate clinical studies using product generated by a manufacturing process designed with a potential for scalability, this will help decrease the likelihood of delays later in clinical development when the manufacturing process is scaled up.	or rare diseases. Well-understood and characterized process changes for viral vectors such as scale-up or changing/adding manufacturing sites using the same manufacturing process during late-stage development should be a low risk if accompanied by a strong analytical comparability package. • Please clarify whether CPV can be introduced during PPQ and be considered as supporting change management during BLA submission review. • We also request information on ways sponsors can receive Agency feedback on CMC issues during development to assist in keeping pace with expedited clinical development.	211.22, 211.100, 211.110(a) and 211.165).**]**
143-149	For both investigational products subject to 21 CFR part 211 and licensed products, you must evaluate data at least once a year to determine if changes in product specifications or manufacturing or control procedures are needed to maintain the quality standards of the product, even when no manufacturing changes are undertaken (21 CFR 210.2, 211.180(e) and	• With respect to the statement that data "must" be evaluated at least once per year, the specific relevance of the citation 21 CFR 210.2 is not immediately clear and some of the citation could be confusing and unhelpful in serving a purpose for this guidance.	

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	601.2(d)). Data trend analysis throughout product development can also be useful for verifying that manufacturing changes do not lead to shifts in manufacturing consistency over time.	• Annual product reviews are not required for investigational products. • 21 CFR 210.2(c) states: An investigational drug for use in a phase 1 study, as described in § 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 U.S.C. 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in § 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211. • It seems the purpose for this citation is to clarify that sponsors should remember that phase-appropriate GMPs should be in	

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		place and consider this in the need for a once-a-year evaluation. Due to the complexity of the multiple references to the CFRs, which then in turn refer to other CFRs/regulations, this point is lost in the guidance. We recommend deleting this specific regulation citation or providing additional clarity by touching on the concept of "phase appropriate GMPs" and including a reference to the July 2008 FDA Guidance: Current Good Manufacturing Practice for Phase 1 Investigational Drugs. • Please clarify whether medical devices used for delivery or to facilitate therapeutic action are in the scope of annual reviews.	
B. Stability and Delivery Device Compatibility			
156-157	DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, or shipping conditions.	• Storage temperature should also be part of this assessment. • Please describe alternate options for autologous products where sufficient material does not exist to perform comprehensive stability studies, including the criteria that should be considered when	DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, **[storage temperature]** or shipping conditions.

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		designing an autologous product study that has material constraints.	
169-177	Many CGT products are stored frozen for a significant length of time. Accelerated stability studies performed under stress conditions may be useful for identifying stability-indicating attributes, but shelf life should be based on real-time stability data obtained at the long-term storage condition. Generating real-time long-term stability data can delay product development, especially when manufacturing changes that have the potential to adversely affect stability are implemented during late stages of product development. For post-licensure manufacturing changes, there may be a need to generate real-time stability data with the post-change product to demonstrate a lack of adverse effect on product quality, and generating these data could severely delay the implementation of the manufacturing change.	• We request clarification as to whether and how accelerated studies may be leveraged to support manufacturing changes. • This recommendation appears to be specific for the DP, but CGT products have other materials which may have process changes, i.e., mRNA or gRNA. Please clarify which components need end of shelf-life data and explain how to leverage platform knowledge for items such as mRNA and/or gRNA. • This section should provide flexibility to provide alternative approaches – especially for product stored at -70 deg C or lower temperatures (e.g., <-120°C, where enzymatic processes are not expected to occur as there is no liquid water). • Please also comment on the possibility of using post-change	Many CGT products are stored frozen for a significant length of time. Accelerated stability studies performed under stress conditions may be useful for identifying stability-indicating attributes, [**evaluating temperature excursions, and trending analysis**]~~but shelf life should be based on~~ Real-time stability data obtained at the long-term storage condition [**are required for shelf-life setting**]. [**Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of pre-change and post-change product.**] Generating real-time long-term stability data can delay product development, especially when manufacturing changes that have the potential to adversely affect stability are implemented during late stages of product development. For post-

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		representative lots to support stability and how much stability data would be expected to support the change. • We recommend re-writing this section to incorporate language supportive of science and risk-based approaches and leveraging the totality of the data/knowledge (e.g., accelerated, stress, long term, platform knowledge, in-use stability studies, or other relevant supportive studies) into this section • For investigational products, initial shelf-life is often provisional, since little to no long-term data is available at the IND opening, and is supported by accelerated or other stability data.	licensure manufacturing changes, there may be a need to generate real-time stability data with the post-change product to demonstrate a lack of adverse effect on product quality. [**However, to support comparability, full real time stability studies are not required in support of the shelf-life claim. Dedicated stability studies under accelerated or stress conditions can be of value to identify possible differences. For cells with very short shelf-life, real time stability studies are expected,]** and generating these data could severely delay the implementation of the manufacturing change.
C. Nonclinical Studies			
General comments		It would be helpful to describe situations in which surrogate cells may be used for non-clinical comparability studies. Please provide additional information on the need for similarity of nonclinical study designs (e.g., species of animal, disease model, etc.)? Is it acceptable to	

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		modify the nonclinical study design based on product understanding, or is the expectation to repeat nonclinical studies from early in the development process in order to support later-stage manufacturing changes?	

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181-185	Nonclinical studies may be needed to support manufacturing changes for an investigational product after clinical studies have been initiated (Ref. 8), or for a licensed product (21 CFR 601.12(a)(2)). If analytical studies alone are insufficient to determine the impact of the manufacturing changes on CGT product quality, then nonclinical studies may contribute to a demonstration of comparability.	• Please clarify what is meant by "non-clinical" here. We assume nonclinical studies refers to animal studies and alternatives to animal studies, as defined in the amended Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), which could be clarified by referencing this statute. • Please provide additional guidance and some examples to help sponsors determine whether analytical studies are sufficient and explain how nonclinical studies may contribute to a demonstration of comparability. • In addition to reference 8, consider adding a reference to this draft guidance document: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products. Draft Guidance for Industry. U.S. Department of Health and Human Services. Food and Drug Administration Center for Biologics Evaluation and Research (March 2022) https://www.fda.gov/regulatory-information/search-fda-guidance-	Move the following statement (line 189-193) from section D Clinical Studies to section C (line 180): **[We recommend that comparability of investigational or licensed CGT products be evaluated through analytical assessment and, if appropriate, nonclinical studies. When applicable and feasible, studies evaluating pharmacokinetic/pharmacodynamic (PK/PD) parameters may be used to contribute evidence in support of comparability between the pre- and post-change products.]**

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		documents/considerations-development-chimeric-antigen-receptor-car-t-cell-product.	

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D. Clinical Studies			
General comments		Examples should be included describing situations when comparability cannot be established through analytical, nonclinical and/or PK/PD studies. A framework similar to that outlined in Q5E Section I.D (1.4) would provide clarity.	
193-198	When comparability cannot be established through analytical, nonclinical, and/or PK/PD studies, the evidence of safety and effectiveness accumulated during clinical investigation with the pre-change product will be insufficient to support a BLA for the post-change product, and the sponsor should contact FDA to discuss plans for additional clinical investigations of the safety and/or effectiveness of the post-change product.	This is an introductory section followed by investigational and licensed products subsections. We recommend that the phrase "will be insufficient to support a BLA" be deleted because the FDA is offering to work with sponsors to avoid this situation.	When comparability cannot be established through analytical, nonclinical, and/or PK/PD studies, ~~the evidence of safety and effectiveness accumulated during clinical investigation with the pre-change product will be insufficient to support a BLA for the post-change product, and~~ the sponsor should contact FDA to discuss plans for additional clinical investigations of the safety and/or effectiveness of the post-change product.
202-209	If analytical and/or nonclinical comparability studies are insufficient to assure that a manufacturing change will not adversely affect safety, then the sponsor should discuss with the FDA (section VII of this guidance) their plans for safety evaluation of the post-change product, which may include conducting new clinical	What is the request/recommendation--considering flexibility for products that treat rare diseases?	

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	studies and/or incorporating additional safeguard measures and safety evaluations in ongoing clinical studies. For example, it may be appropriate to consider broadening the scope of the adverse events of special interest, staggering enrollment of subjects, modifying study stopping rules, and conducting additional dose-finding studies.		
211-214	If comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an adverse impact on product effectiveness, then the sponsor will need to evaluate the effectiveness of the post-change product in clinical studies to support a BLA for the post-change product.	Edit recommended to better align with the staged approach to comparability and to reflect that efficacy is studied during Phase 3. Please also clarify what is meant by this statement. Under what circumstances would comparability studies be insufficient to exclude an adverse impact on product effectiveness? Are there methods that are presumed to be inadequate as a matter of course? Is there a mechanism to assess the suitability of the tools before data are generated? How are sponsors to evaluate whether the studies are sufficient? How is product effectiveness defined?	If [**the analytical and / or nonclinical]** comparability studies demonstrate that the manufacturing change does not adversely affect product safety but are insufficient to exclude an adverse impact on product effectiveness, then the sponsor will need to evaluate the effectiveness of the post-change product **[as part of pivotal or Phase 3]** ~~in~~ clinical studies to support a BLA for the post-change product.
218-222	In addition, evidence demonstrating a prospect of direct benefit of a pre-change investigational CGT product to pediatric subjects, as required for studies conducted in accordance with 21 CFR 50.52, may not be adequate to demonstrate prospect of	• The sentence is unclear as written. We recommend replacing the conclusion that "may not be adequate" to state that 21 CFR 50.52 applies as well when children are part of clinical investigations.	In addition, ~~evidence demonstrating a prospect of direct benefit of a pre-change investigational CGT product to pediatric subjects, as required~~ **[the requirements for**

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	direct benefit with respect to the post-change product.	• FDA should clarify how the direct benefit requirement for pediatric studies differs from evaluating impact on effectiveness as part of the comparability analysis.	**conducting] studies ~~conducted~~ in children in accordance with 21 CFR 50.52,** ~~may not be adequate to demonstrate prospect of direct benefit with respect to the post-change product~~ **[applies to demonstrate evidence of the prospect of direct benefit for the individual subject.]**
225-227	Such modifications could include an increase in the number of subjects exposed to the post-change product and initiation of new clinical studies with the post-change product.	Please replace "new clinical studies" with specific recommendations.	Such modifications to **[obtain additional clinical data]** could include an increase in the number of subjects exposed to the post-change product, **[PK/PD, or clinical bridging studies.]** ~~and initiation of new clinical studies with the post-change product~~.
227-229	In the case of pediatric studies for which a prospect of direct benefit is required, nonclinical data demonstrating prospect of benefit may be sufficient during early-stage clinical development.	It is unclear if this sentence means that nonclinical data demonstrating prospect of benefit may be sufficient during early-stage clinical development to demonstrate comparability between pre-and post-change investigational product with respect to clinical effectiveness.	

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231-233	If you wish to pool clinical data from subjects treated with the post-change product and subjects treated with the pre-change product, you should demonstrate that the products are comparable, and justify that the clinical study designs are appropriate for pooling.	Clarify that justification that the clinical study designs are appropriate for pooling is a separate recommendation. Consider referencing to Section D under Clinical Studies, line 202, which explains how to pool when there is not comparability. Examples of the kinds of designs that are appropriate for pooling would be helpful.	If you wish to pool clinical data from subjects treated with the post-change product and subjects treated with the pre-change product, you should demonstrate that the products are comparable and justify that the clinical study designs are appropriate for pooling. **[Meeting both these criteria is critical to pooling data from pre- and post-change product in support of licensure.]**
IV. Regulatory Reporting of Manufacturing Changes			
251-252	Applicants must notify FDA of manufacturing changes through a BLA supplement or annual report in accordance with 21 CFR 601.12 (Ref. 6).	The annual report requirement should only apply to licensed products.	**[For licensed products],** **a**pplicants must notify FDA of manufacturing changes through a BLA supplement or annual report in accordance with 21 CFR 601.12 (Ref. 6).
A. CMC Changes Requiring a New IND Submission			
General comment	[CMC changes requiring a new IND submission]	All examples of changes requiring new IND submission seem to be related to cell therapies. Are there examples related to gene therapy products that should be captured?	

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267-269	Some changes can fundamentally alter the design or nature of the product, resulting in a new product.	Clarification to replace "some changes" to describe as intentional changes to alter product.	~~Some~~ Changes ~~can fundamentally~~ **[that intentionally]** alter the design or nature of the product~~,~~ ~~resulting~~ **[may result]** in a new product.
273-274	Change in the cellular starting material of a cellular product (e.g., allogeneic vs. autologous donor; adipose-derived cells vs. umbilical cord-derived cells)	FDA should consider that the cell lines have been used in clinic, have an established safety profile, would be used on a consistent patient population, could be minimally gene edited and should not need a new IND.	
275-276	Change to the types of cells in a cellular product (e.g., mixture of CD4+ and CD8+ T cells instead of solely CD4+ T cells)	• We recommend making a distinction between intentional change to the types of cells in a cellular product vs. natural variability that occurs in a cellular product that is comprised of a mixture. • FDA should consider these process optimizations that cause cell subpopulation shifts optimizations to improve the product profile and they should not require a new IND.	Change ~~to the types of cells in a cellular product~~ **[in the design of a cellular product to target different types of cells]** (e.g., mixture of CD4+ and CD8+ T cells instead of solely CD4+ T cells)

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282-283	Change to the sequence of a transgene or addition of a transgene (e.g., changes to the intracellular signaling domain of a chimeric antigen receptor)	It would be preferable if the guidance more specifically describes the type of change instead of referring to "change to the sequence of the transgene."	Change to the sequence of a transgene or addition of a transgene ~~(e.g. changes to the intracellular signaling domain of a chimeric antigen receptor)~~ **[that impacts the mechanism of action or intended therapeutic effect, or if adequate comparability cannot be demonstrated by analytical, nonclinical and/or clinical studies. (e.g. Protein-coding changes such as the addition of a domain or second transgene)]**
B. Reporting Manufacturing Changes to an IND			
299-302	The sponsor should submit such amendments for FDA review prior to use of the changed product in clinical investigations. The FDA will review data or study reports submitted to support the change, and may provide comments (section V of this guidance).	• For investigational products, is there a time period for FDA review that sponsors should plan for before use of the changed product in clinical investigations?	
306-310	If a manufacturing change has the potential to adversely affect safety, and if you do not submit evidence to your IND demonstrating that the post-change product has an acceptable safety profile, then your IND may be placed on clinical hold at any phase of clinical development (21 CFR 312.42(b)(1)(i), 21 CFR 312.42(b)(1)(iv), and 21 CFR 312.42(b)(2)(i)).	What if a sponsor has already started dosing the post-change material in the clinic? Please see previous comment on timing of FDA review comments.	

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311-315	If these data do not allow for a conclusive determination that the manufacturing change has no adverse effect on product quality as it relates to safety, then you should consider performing a toxicology study to evaluate whether the post-change product has an acceptable safety profile.	• The recommendation that a toxicology study should be conducted could be interpreted as recommending an animal study. We suggest aligning this section with the other sections in the guidance and refer to using the broader terminology of "nonclinical study," since other nonclinical studies such as in-vitro or in-silico could also be applicable. • "Conclusive" is too vague and should be removed, or defined in the alternative.	If these data do not allow for a ~~conclusive~~ determination that the manufacturing change has no adverse effect on product quality as it relates to safety, then you should consider performing ~~a toxicology~~ **[nonclinical studies]** to evaluate whether the post-change product has an acceptable safety profile.
320-324	FDA's review of an IND submission for a phase 2 or 3 clinical study includes assessing the likelihood that the study will yield data capable of meeting statutory standards for marketing approval (21 CFR 312.22(a)), and a phase 2 or 3 study may be placed on clinical hold if the plan or protocol for the study is clearly deficient in design to meet its stated objectives (21 CFR 312.42(b)(2)(ii)).	• FDA should clarify that if a comparability protocol is submitted via an IND amendment requesting feedback, and the change has not yet been implemented, then a clinical hold will not be issued. Since the change is not yet implemented, there is no risk to patient safety.	
325-331	If, for example, a phase 3 study intended to provide substantial evidence of effectiveness to support a BLA for a post-change product uses lots of both pre- and post-change product, but those products are not comparable, then the study may lack statistical power to demonstrate	Sponsors typically have limited data so it is rarely possible to do any studies – analytical/nonclinical/clinical – that have "statistical power to demonstrate effectiveness of the post-change product". Instead, totality of risk assessment, analytical, nonclinical,	If, for example, a phase 3 study intended to provide substantial evidence of effectiveness to support a BLA for a post-change product uses lots of both pre- and post-change product, ~~but those products are not comparable,~~

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	effectiveness of the post-change product. Such a study may be considered clearly deficient in design to meet its stated objectives and placed on clinical hold if the IND submission does not provide evidence demonstrating comparability of the pre- and post-change products.	clinical data should be evaluated for suitability of using pre- and post-change product in phase 3.	~~then the study may lack statistical power to demonstrate effectiveness of the post-change product. Such a study may be considered clearly deficient in design to meet its stated objectives and placed on clinical hold if the IND submission does not provide evidence demonstrating comparability of the pre- and post-change products.~~ **[the sponsor is encouraged to work with the FDA on an agreeable approach to progressing with a phase 3 study using both pre- and post- change product. Comparability protocols may be submitted as an amendment to the IND to gain alignment with the FDA on the study design prior to execution. The comparability study report should be submitted as a subsequent amendment.]**
C. Reporting Manufacturing Changes to a BLA			
346-349	When reporting these changes, your supplement or annual report should include a risk assessment report and must include data from appropriate studies performed to evaluate the effect of the changes on product quality as required	The recommended risk assessment report is onerous. We recommend that a risk evaluation/statement should be allowed in lieu of the report. The risk assessment summary/statement could be placed in Module 1.	

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	under 21 CFR 601.12(b)(3)(iv)-349 (v), 21 CFR 601.12(c)(3), or 21 CFR 601.12(d)(3)(ii) (Ref. 6).		
V. Comparability Assessment and Report			
General comments		We request additional clarity in this section regarding the kind of quality change that would constitute a "different product" and that the recommendations be reconciled with relevant points outlined in "Chemistry Manufacturing and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)", Section V.A.2.f (Manufacturing Process Development) that discuss assessment of differences when process changes are made. Example 1: Cell Therapy: autologous vs allogeneic starting material; Consistent push for process improvements, but this may result in a "different product", which is prohibitive to developers. Example 2: Gene Therapy: Dose considerations (empty/full vector example) – At what point is a "new" product generated?	

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364-371	Comparability Assessment and Report Comparability between the pre-change and post-change products is generally demonstrated by 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 quality, such that there is a significant benefit in effectiveness and/or safety, then the post-change product may be considered a different product, and therefore not comparable to the pre-change product.	• Pre- and post- change product not being comparable should not automatically mean that the post-change product is a "different" product. • Would like clarification to the context in which manufacturing changes introduced to improve the overall quality of a tissue-engineered product could result in a "different product" determination versus a "same but not comparable product" pre-post change. • This is generally inconsistent with ICH and other language within this guidance (see, e.g., Lines 625-627). FDA should provide examples of what safety improvements may result in a new product. • Additionally, if efficacy is improved, then clinical strategy may be implemented (e.g. modified dosing). We suggest that this section be aligned with Section III.B of the guidance, and that the guidance recommend that sponsors contact FDA if significant change in efficacy is observed.	However, if the change is intended to improve product quality, such that there is a significant benefit in effectiveness and/or safety, then the post-change product may be considered ~~a different product, and therefore~~ not comparable to the pre-change product. **[For example:** **- For a licensed product, the approved dose would result in a risk to patient safety due to an increase in potency.** **- For an investigational product, potency will be increased in such a way that cannot be proportionately controlled by a defined reduction in dose.** **- Replacement of a manual process with an automated process, resulting in clinically relevant impacts to CQAs.]**

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		• This section seems to assume a comparability study report will be submitted. An alternative approach is to summarize the data from the comparability study report in S.2.6 or P.2.3, and we ask that FDA clarify that either approach is acceptable.	

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377-379	When submitting a comparability study report to an IND or BLA, you should include a cover letter or reviewer's guide outlining the submission contents to streamline the FDA review process.	Provision of the final internal study report may result in delays to the submission, which may cause delays to supply. We suggest flexibility in reporting; and the ability to include meeting minutes with the package.	When submitting **[details for the completed]** ~~a~~ comparability study to an IND or BLA, you should include a cover letter or reviewer's guide outlining the submission contents to streamline the FDA review process.
383-386	When submitting a comparability study report to your IND, for example, it is helpful to describe the stage of clinical development, the number of subjects to whom the pre-change product will be administered, and the number of subjects expected to receive the post-change product.	• It may not be possible to describe the exact number of subjects to receive the pre- and post-change product. • Provision of the final internal study report may result in delays to the submission, which may cause delays to supply.	When submitting [details for the completed] ~~a~~ comparability study ~~report~~ to your IND, for example, it is helpful to describe the stage of clinical development, the **[estimated]** number of subjects to whom the pre-change product will be administered, and the **[estimated]** number of subjects expected to receive the post-change product.
391-392	Comparability study reports should be submitted to CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the BLA or IND, as appropriate.	• Provision of the final internal study report may result in delays to the submission, which may cause delays to supply. • S2.6 or P2.3 usually include summary of comparability study, not the reports. • Comparability reports are rarely submitted without updates to other relevant quality sections.	**[Details for the]** comparability study should be [included in] CTD sections 3.2.S.2.6 or 3.2.P.2.3 of the BLA or IND, **[along with updates to other quality sections]** as appropriate.

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392-394	Your comparability study report should evaluate the totality of the comparability data, including historical manufacturing data, to determine if the pre- and post-change products are comparable.	Providing the final internal study report may result in delays to the submission, which may cause delays to supply. Historical manufacturing data may be limited in early/late and even in the commercial environments. Rather than a final report, sponsors should be permitted to provide a justification for selecting representative batches to be included as part of the comparability package. The justification may include historical manufacturing data if it is available.	The details provided for your comparability study should include an evaluation of the totality of the comparability data, including historical manufacturing data, to determine if the pre- and post-change products are comparable.
396-399	You should also include a discussion of any potential limitations of the study. If a product quality attribute does not meet the pre-defined acceptance criterion for comparability, but you still consider the pre- and post-change products to be comparable, you should provide justification and/or additional scientific information to support your conclusion for FDA review	This statement is contradictory to previous sections defining "comparable." We suggest adding a statement with respect to utilization of non-clinical studies here to further support analytical comparability. Examples and elaboration would be helpful.	You should also include a discussion of any potential limitations of the study. If a product quality attribute does not meet the pre-defined acceptance criterion for comparability, but you still consider the pre- and post-change products to be comparable, you should provide justification and/or additional scientific information to support your conclusion for FDA review **[the justification may include, for example, toxicology data or clinical study data with the pre-change product.]**

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A. Risk Assessment			
405-408	To evaluate whether the proposed manufacturing change may impact product quality, you should conduct a detailed risk assessment as recommended in International Council for Harmonisation (ICH) Q9 dated June 2006 (Ref. 1).	The scope of risk assessment should depend on the development stage. For early process changes (early tox and clinical batches), the risk assessment is limited because of the limited understanding of the process.	
412	We recognize that risk assessment for changes to the manufacturing of CGT products may be more challenging than for other product types because the effects of manufacturing changes are often difficult to predict for these complex products	We agree with this statement, however no alternative path forward is proposed. We suggest adding a potential path or paths forward.	
419-422	Transferring a manufacturing process to a new manufacturing facility is generally considered a major change that may require extensive comparability evaluation in addition to technology transfer, because it may involve changes to the manufacturing process, shipping, manufacturing equipment, testing equipment, and operators.	• Turnover of operators at a licensed commercial site would not be considered a manufacturing change. Consider replacing "operators" with "training program" or a similar concept. • Please provide guidance for onboarding manufacturing facilities early in clinical development, when data for an “extensive comparability evaluation” is not available by describing what technology transfer, onboarding data, and results are minimally acceptable.	Transferring a manufacturing process to a new manufacturing facility is generally considered a major change that may require **[an]** extensive comparability evaluation in addition to technology transfer, because it may involve changes to the manufacturing process, shipping, manufacturing equipment, **[and]** testing equipment~~, and operators~~.

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423-424	Performing a thorough risk assessment, including consideration of method equivalence and CPPs, is essential when transferring a manufacturing process to a new facility.	Please provide clarification regarding risk assessment component.	Performing a thorough risk assessment, including consideration of method equivalence and **[potential impact to]** CPPs, is essential when transferring a manufacturing process to a new facility.

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428-433	We recommend that you take a stepwise approach to select all quality attributes and process parameters to be evaluated in a comparability study; first, you should determine which attributes might be affected by the particular change, and then you should assign a score to each attribute based on the probability, severity, and detectability of the risk.	• Mentioning process parameters here may cause confusion and we propose that this sentence only mention (p)CQAs.	We recommend that you ~~take a stepwise, risk-based approach to select all quality attributes and process parameters~~ **[select all (potential) critical quality attributes (CQAs)]** to be evaluated in a comparability study **[as these can have an impact on efficacy and patient safety].**

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433-436	Manufacturing changes that are determined to have a high risk to product quality should be supported by an extensive analytical comparability study, while it may be possible to evaluate low-risk changes using a more focused approach.	• This implies that low-risk (but still non-zero risk) changes may not need a comparability study and could be included in an annual report. Is that accurate? • For clarity, we recommend further context and explanation regarding "a more focused approach".	Manufacturing changes that are determined to have a high risk to product quality should be supported by an extensive analytical comparability study, while it may be possible to evaluate low-risk changes using a more focused **[analytical]** approach **[or justification by risk assessment alone.]**
440-445	Please note that relying solely on established release tests and in-process controls is generally insufficient to assess the impact of manufacturing changes. Therefore, we recommend that you consider the potential impact of manufacturing changes on quality attributes that are not routinely evaluated by established release tests and process controls, and consider additional characterization studies as appropriate.	The Agency should provide examples of additional characterization studies and guidance on FDA's perspective on evaluating data for comparability that may not have historical context or is highly complex, where focused elements are used while collateral elements are not interpretable for comparability (such as genomic sequencing).	
448-451	In your risk assessment, you should justify how the selected quality attributes and process parameters can be used to comprehensively evaluate the potential effect of the change on product quality.	This sentence's mention of process parameters may cause confusion and we propose that it only mention (p)CQAs.	In your risk assessment, you should justify how the selected **[(p)CQAs]** ~~quality attributes and process parameters~~ can be used to comprehensively evaluate the potential effect of the change on product quality **[and therefore, efficacy and safety. Using previous knowledge of (p)CPPs, the potential impact on (p)CQA due to changes to process**

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			parameters can inform the study design including sampling plan.]
453-455	Your risk assessment should also inform the statistical approach to comparability. Higher risk attributes typically warrant a more stringent statistical analysis than lower risk attributes.	• Limited data poses significant challenges as stated on line 519. We propose the following in recognition of this point. • Provide examples of statistical approaches that would apply to higher risk attributes.	Your risk assessment should also inform the statistical approach to comparability **[when sufficient amounts of data are available and your rationale for the choice of the statistical approach.]…**
455-457	Side-by-side or graphical presentations (such as dot plot) to allow visual comparison, in lieu of statistical analysis, may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change.	Suggest revised wording since plots of data can provide valuable and easy to visualize information on the distribution of results. This approach may also be sufficient when there are not enough data to perform a stringent statistical analysis as in the case where only a few batches have been manufactured. Please provide additional clarification regarding the statistical methods that can be used for comparison for attributes at high risk. For example, is there applicable guidance on acceptable statistical methods that can be referenced here?	Side-by-side or graphical presentations (such as dot plot) to allow visual comparison**s of the results, and distribution of the results, can be informative and alone**~~, in lieu of statistical analysis,~~ may be sufficient for characterization of attributes at low risk of being impacted by a manufacturing change[**, or in cases where limited numbers of batches are available for pre-change product or post-change product and there are not enough data to perform a stringent statistical analysis**].

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459-462	It is important to note that a manufacturing change may affect product stability even if the change has no other effect on product quality or process performance. As discussed in section III.B, you should assess the potential risk to product stability and delivery device compatibility.	• The statement about the potential impact to stability even if there is no impact to product quality or process performance is rather broad and vague. The statement could be misinterpreted to mean that any change could affect stability and lead to unrealistic expectations for comparability. This seems to undermine guidelines provided earlier in the section regarding risk assessment and assumes that in all cases there is little product understanding. • For clarity, we suggest that the guidance explicitly state that this comment refers to assessing the impact to (p)CQAs only evident with storage.	It is important to note that [**the impact on quality attributes may not be evident until the product is stored. Therefore, the]** ~~a~~ manufacturing change may affect product stability even if the change has no other effect on product quality or process performance….
464-466	Finally, if multiple changes are to be implemented simultaneously, we recommend that you assess the risk of each individual change and the potential	The Agency should acknowledge that changes may not be able to be independently assessed because they collectively have to be used to provide	

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	cumulative effect of the changes on product quality.	the intended result and this should be taken into account.	
B. Analytical Comparability Study Design			
General comments		This section should include discussion of a phase-appropriate approach to study design and statistical methods/analysis. See also comment for Section III, Lines 99-100.	
475-478	Prior to conducting a comparability study for a CGT product that is licensed or being studied under an IND, we recommend that you submit a detailed study protocol (comparability protocol) and request feedback from the FDA (section VII of this guidance) on the study design and statistical approach.	We request clarity on how a meeting request or an amendment to IND should be used to submit the protocol for review.	
502-506	If it is not feasible to manufacture full-scale lots for the comparability study, you should perform data-driven risk assessment of CPPs, CQAs (including potency), and other relevant product characteristics to justify that scaling down the manufacturing process provides for an adequate evaluation of the effects of the manufacturing change on product quality.	FDA should provide examples of when a scale down model is not adequate or acceptable.	

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508-512	A comparability study may be designed as a comparison of historical pre-change testing data to newer data from post-change lots. Such a study design requires that the analytical test methods are equivalent across product lots to provide interpretable data. If analytical methods have changed over time, retained samples from pre-change lots may need to be reanalyzed using the current analytical methods.	Method optimization is an ongoing activity through product development. Data that demonstrate an optimized method are the same for the purposes of their use in the process should be sufficient for the method's continued use. Testing retains samples with the same, optimized method should be considered under exceptional circumstances only. Bridging data tested by pre- and post- change method, using samples specifically created for the study (non-retains) are a suitable option to demonstrate assay performance.	
513-515	Ideally, the only differences between the historical pre-change lots and the post-change lots should be the manufacturing changes that are being evaluated in the comparability study.	This contradicts previous Agency feedback. There may be cases when it is desirable to show comparability across more than one process.	
515-519	If the pre-change product was manufactured using multiple processes or facilities, comparability should be demonstrated across the pre-change lots before they are included in a comparability study evaluating a newly proposed change.	• Please comment on using pre-change lots across the lifecycle if previous changes have been part of comparability studies and were demonstrated to have no impact on safety and effectiveness, especially if the number of available lots is small. • Please confirm that the same products manufactured at different	

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		facilities, using the same process, particularly in commercial production where the products have undergone regulatory scrutiny, are inherently comparable and should not have to undergo an additional comparability study before being considered for a comparability study data set.	

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519-524	For some CGT products, the number of lots may be very small due to, for example, limited manufacturing for rare disease indications, rapid development timelines during clinical studies, or difficulty obtaining cellular starting materials from an adequate number of donors. An insufficient number of lots could compromise statistical power and be insufficient to demonstrate comparability, particularly if there is high lot-to-lot variability, as discussed later in section V.E. of this guidance.	• The statements here acknowledge the challenges relating to insufficient availability of lots but offer no guidance or suggestions on how to manage them as they relate to comparability. We suggest that the Agency provide examples for those sponsors new to the industry or for sponsors described in the section. • Again, if the improved product is considered a different product, what is the development path for the improved product? • We suggest adding the use of process development and engineering runs as described in the section *Special Consideration for Vectors Used for ex vivo Cell Modification*.	For some CGT products, the number of lots may be very small due to, for example, limited manufacturing for rare disease indications, rapid development timelines during clinical studies, or difficulty obtaining cellular starting materials from an adequate number of donors. An insufficient number of lots could compromise statistical power and be insufficient to demonstrate comparability, particularly if there is high lot-to-lot variability, as discussed later in section V.E. of this guidance. **[It may be appropriate for comparability studies to include vector lots that were manufactured during process development or engineering runs. Sponsors are encouraged to submit comparability protocols to seek the FDA's feedback on study design ahead of executing studies.]**

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526	Special considerations for products derived from a variable cellular starting material	We endorse the use of surrogate or healthy donor materials wherever possible, in particular for autologous applications.	
533-534	We recommend that you use a split-source study design, wherever possible.	The previous section recommends full-scale runs whenever possible, but in this section a split-source design is suggested. These recommendations are at odds with each other since split-source runs are nearly always smaller scale.	
538-540	As described in *Comparability acceptance criteria* later in this section, the results obtained from the split runs should meet the in-process and release specifications and be representative of relevant historical data.	• We request clarification regarding whether results indicate each individual sample as a result or whether any pooling of results is acceptable. • We also request FDA to clarify whether every single result is representative of a batch and how FDA recommends that sponsors treat the data.	As described in Comparability acceptance criteria later in this section, **[each individual sample]** results obtained from the split runs should meet the in-process and release specifications and be representative of relevant historical data. **[Note: where comparability criteria are defined for combined sample results, a justification for this approach should be provided.]**
541-545	If a split-source study design is not possible, and it is already known that CQAs for a specific product and clinical indication can vary within a wide range without any adverse impact on product quality, then accordingly, it may be acceptable to set	• The sentence should be revised to provide more information about designing a study that does not include a split-source design. • Can an independent analysis be used with appropriate justification,	If a split-source study design is not possible, ~~and~~ **[the strategy for generating meaningful results for comparability assessment should be carefully considered. However, if]** it is already known

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	wide acceptance criteria for comparability studies, which would reduce the number of lots for the study.	i.e. in the case where donor variance is a small component of the overall variance for an attribute?	that CQAs for a specific product and clinical indication can vary within a wide range without any adverse impact on product quality, then accordingly, it may be acceptable to set wide acceptance criteria for comparability studies. ~~which would reduce the number of~~ **[This may also require fewer]** lots for the study **[compared to a study to confirm limited variability of CQAs.]**
564-569	*Special consideration for vectors used for ex vivo cell modification* GT vectors[8] used for ex vivo cell modification must be manufactured in compliance with current good manufacturing practices (cGMP) under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as appropriate for the stage of development (Ref. 11). *** FN8: 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	• We request that FDA provide input on how to treat other critical components for *ex vivo* cell modification, e.g. small molecule media additives, proprietary biologics (e.g. RNPs), or oligonucleotides (mRNA/gRNA), cell banks and plasmids (including bacterial cell banks) used to manufacture Vector used for ex-vivo GT. • Analytical procedures may not be relevant or current and therefore are not always transferred to a new manufacturing site or used for a new vector process. Testing for a new process or facility can occur with current methods used on historic samples that are not also	

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	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)	contemporaneously tested by the previous methods. FDA should clarify the expectations during the overall comparability assessment, especially if vectors are not the final drug product. • The footnote may include items related to gene therapies such as electroporation and lipid nanoparticles.	
577-580	In addition, the effect of the vector manufacturing change on the quality of the ex vivo gene-modified cells (DS and/or DP) should be evaluated in an analytical comparability study using an adequate number of vector, DS and/or DP lots.	Some changes have low risk impact on the ex vivo cell modification. Therefore, it should not be required that ex-vivo cell modification be evaluated if this is the case.	In addition, the effect of the vector manufacturing change on the quality of the ex vivo gene-modified cells (DS and/or DP) should be evaluated in an analytical comparability study using an adequate number of vector, DS and/or DP lots**[,except in the case where the risk assessment has indicated that the quality of the ex vivo gene modified cells would not be impacted].**
582-587	The number of vector lots available for comparability studies may be small in situations where each lot of vector is sufficient for the manufacture of large numbers of DP lots. In such cases, it may be appropriate for comparability studies to include vector lots that were manufactured during process development or engineering	The situation of having a limited number of lots available for comparability is not unique to *ex vivo* vectors. This is a common situation for CGT products, especially those for rare diseases.	

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	runs, if manufacture of these vector lots is similar to the manufacture of the vector lots used to manufacture DP for clinical studies.		
594-596	The biological activity of CGT products can be highly sensitive to manufacturing changes. Therefore, we recommend that a quantitative potency assay (Ref. 12) be included when performing analytical comparability studies.	We recommend that the Agency not require all potency methods to be quantitative and employ a flexible approach to non-MOA features of complex products (i.e., armor).	
596-599	You may wish to consider using several analytical methods to evaluate potency if the routinely used analytical method is imprecise or unable to assess all aspects of the product's MOA that might be affected by the manufacturing change.	• We are not aware of any potency methods that can possibly assess all aspects of product MOA. • We also suggest clarifying that if a potency matrix is used, the assay that is the most likely to detect a change "takes precedence" in establishing comparability. • We also point out that it could be uncommonly difficult to establish a quantitative potency assay for a tissue-engineered construct. Further, opportunity to test potency of a human tissue engineered product in an animal model may be severely restricted. Please provide some guidance on how to measure potency for a tissue engineered product that could support a comparability determination.	You may wish to consider using several analytical methods to evaluate potency if the routinely used analytical method is imprecise or unable to assess ~~all~~ aspects of the product's MOA that might be affected by the manufacturing change.

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610-611	Yet, exclusion of potency analysis from a comparability evaluation compromises the conclusions drawn from a comparability study.	Would this also include products that have features that do not directly impact MOA, but potentially enhance or provide durability for MOA?	
611-613	To avoid this situation, we recommend that samples be retained from all lots to facilitate future analysis of potency to support comparability.	• Does this include PD lots or does the recommendation only apply to engineering lots? A limitation of this approach is that potency may decline over time. Also, it may be possible to demonstrate equivalency in terms of potency prior to the determination of final release criteria. • Retaining samples for testing is not always possible for fresh products, since freezing or otherwise storing DP inherently changes the product, rendering testing suspect. Can the Agency provide recommendations on how to implement potency testing for fresh products when determining whether the correct assay(s) are hampered by the understanding of MOA versus safety and effectiveness?	

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619-621	A manufacturing change that significantly increases potency, even if intentional, may raise safety concerns. In such cases, if you are unable to demonstrate that the change will not adversely affect safety, the post-change product will not be considered comparable to the pre-change product.	• A process change that improves purity or potency is comparable in that all the key quality and process attributes apply. "Not to be considered comparable" provides a negative connotation which suggests a product is sub-standard. FDA should consider different language to describe how a deliberately introduced benefit does not unnecessarily impair its clinical development.	A manufacturing change that significantly increases potency, even if intentional, may raise safety concerns. ~~In such cases, if you are unable to demonstrate that the change will not adversely affect safety, the post-change product will not be considered comparable to the pre-change product.~~ **[Evaluate all of the CQAs, characterization data, as well as relevant nonclinical and clinical information to determine the acceptability of the product in terms of product safety.]**
625-627	It is not necessary for the measurements of pre- and post-change CQAs to be identical to reach a conclusion of comparability if there is evidence demonstrating that there is no adverse impact of the change on product quality.	This statement is in conflict with earlier language stating that significant improvement of product safety/efficacy may result in un-comparable product ("CQAs do not need to be identical, so long as there is no **adverse** impact to product quality")	
638	An equivalence approach is often appropriate for evaluating comparability of CQAs	As we have mentioned, one of the significant challenges to this approach is limited data.	**[When sufficient data are available,] a**n equivalence approach is often appropriate for evaluating comparability of CQAs.

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640-641	For normally distributed data, the equivalence margin should be defined as the maximum acceptable difference in population means.	We request additional information on what sponsors should do if the data are not normally distributed or this distribution is yet to be determined.	
642	Exceeding this margin would be interpreted as an adverse effect of the post-change manufacturing process on product quality.	If margins are exceeded, that does not necessarily mean that there is an adverse effect of the post-change manufacturing process on product quality.	~~Exceeding this~~ **[When the]** margin ~~would be interpreted as an adverse effect of the post-change~~ **[is exceeded, the products would not be considered equivalent.]**
647 - 649	The quality range approach can potentially be used for attributes with various risk levels, but higher-risk attributes should be evaluated using the more rigorous equivalence approach.	What is a "more rigorous equivalence approach" that could be applied in such a situation? Please provide example statistical approaches that could be applied.	
655-658	Otherwise, you should ensure that the comparability study is designed with sufficient power by calculating the number of post-change lots needed to demonstrate with high confidence that an appropriate proportion of future lots will fall within the quality range.	We request clarification of what to do when this is not possible. It may not be practical to design a comparability study by calculating the number of post-change lots needed to design the study with sufficient power. The post-change lots may not be able to be dedicated for statistical analysis because they may be needed for clinical supply.	
C. Analytical Methods			

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679-680	We recommend that you provide a tabular listing of the analytical methods and testing sites used in the comparability study.	We recommend that FDA make a minor edit to reflect that testing sites do not need to be provided in tables that would be filed in 3.2.S.2.1 and 3.2.P.3.1 of IND or BLA.	We recommend that you provide a tabular listing of the analytical methods and testing sites used in the comparability study. **[Testing sites do not need to be provided in tables filed in 3.2.S.2.1 or 3.2.P.3.1 of an IND or BLA.]**
682-684	For comparability studies of investigational products, all release assays used to demonstrate comparability should be qualified or validated, depending on phase of clinical study.	Please provide recommendations for specific phases of drug development. Validation requirements for Phase 1 studies are different from the requirements for BLAs.	
686-687	Assays used for extended characterization do not necessarily need to be qualified, but they should be scientifically sound and fit for their intended use, be sufficiently precise to detect meaningful differences in product quality and provide results that are reliable.	Please provide clarity for specific phases of clinical trials because "sufficiently precise" has different meanings dependent on phase of drug development. Does the Agency have specific recommendations on how a Sponsor might define "sufficiently precise"?	
687-690	If not described elsewhere, you should describe sample acquisition (e.g., process step, sample volume, storage temperature) and justify any differences in acquiring samples from the pre-change and post-change manufacturing processes.	This information is too detailed for submission. Method qualification/validation, stability studies, etc., should adequately address these concerns.	~~If not described elsewhere, you should describe sample acquisition (e.g., process step, sample volume, storage temperature) and justify any differences in acquiring samples from the pre-change and post-change manufacturing processes.~~

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700-706	Therefore, it is especially important that the analytical methods used to assess the effect of manufacturing changes on product quality and process control are sufficiently precise. For example, if 5% change in a particular cell marker represents a meaningful change in product quality, then a flow cytometry assay with an intermediate precision of 20% coefficient of variation would not be adequate for evaluating whether there is a meaningful difference in that attribute between the pre-change and post-change products.	• Edit recommended for clarity. • Based on this example, essentially no potency method would be sufficiently precise to detect differences in product quality. There also should be a discussion regarding use of orthogonal methods to develop a more robust assessment of product quality.	… For example, if **[it is known that a]** 5% change in a particular cell marker represents a meaningful change in product quality, then a flow cytometry assay with an intermediate precision of 20% coefficient of variation would not be adequate…
712-715	To provide the most readily interpretable data for a comparability study, we recommend that you perform side-by-side testing of pre-change and post-change product attributes or analyze all samples using the same analytical method performed at the same testing facility.	• Head-to-head testing may not always be available if a commercial kit is discontinued and/or retain vials are limited. ARM requests the Agency note that when this is not possible that the sponsor assess risk and discuss with the Agency. • We note that not all tests such as physiochemical, impurities need to be done side-by-side.	To provide the most readily interpretable data for a comparability study, we recommend that you perform side-by-side **[biological]** testing of pre-change and post-change product attributes or analyze all samples using the same analytical method performed at the same testing facility. **[When this is not possible, sponsors should discuss the appropriate approach with the Agency.]**

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D. Results			
732-735	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.	We suggest including a decision tree with examples of choices of statistical methods.	
E. Statistics			

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745-748	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.	• Lines 745-748 outline difficulties with limited samples and highly variable quality attributes. Lines 800-808 then discuss the use of the TOST procedure. While this procedure is effective protecting AGAINST type I error (α) it may not be useful in the scenario described in lines 745-748. • As noted for Section V.B, Lines 519-524, the situation of having limited material available is noted, then guidance is provided to run statistics with a larger number of lots. It is not feasible for many programs, in particular those for rare diseases, to generate additional lots solely for the purpose of a comparability study. Alternative guidance needs to be provided for these situations. • We recommend further discussion of the statistical or non-statistical methods that might be useful in situations with “only a limited number of samples, when quality attributes are highly variable”.	

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769-775	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 manufacturing changes, especially during late-stage development and after licensure.	Again, we point out that typically limited material is available, but the guidance contemplates running statistics with a larger number of lots. It is not feasible for many programs, in particular those for rare diseases, to generate additional lots solely for the purpose of a comparability study. Alternative guidance needs to be provided for these situations.	
779-786	In such situations, an alternative to improving the precision of the assay would be to reduce measurement uncertainty by performing the assay multiple times independently for each lot and reporting the mean value. Such an approach will improve the statistical power of the comparability analysis for that attribute. It is important to note that the mean of the assay results for each lot should be treated as a single data point when analyzing comparability; it is inappropriate to treat each individual assay result as an independent data point in the comparability analysis.	ARM appreciates this practical suggestion for cases in which there are a limited number of lots. It would be beneficial to include clarification to illustrate how to assess and decide on how many replicates values are required or to provide a reference to the statistical literature.	

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800-808	To evaluate equivalence, you may consider calculating an appropriate confidence interval for the difference between the pre- and post-change data, and conclude equivalence if this confidence interval is within the equivalence margin. When the CQA of interest is a mean value, you may consider using the 'Two-One-Sided Tests procedure' (TOST) or other appropriate statistical method to establish comparability. For some attributes (e.g., impurity, viability), it may be possible to demonstrate that the manufacturing change has no adverse effect on product quality using a one-sided statistical comparison, such as non-inferiority testing or other appropriate method.	• We suggest that FDA reorganize this section for clarity. For example, a decision tree on which type of statistical method would be used in what situations - with more specific examples of methods that may be appropriate, (e.g. prediction interval) would be helpful. • It is unclear how this relates to lines 46-49, which indicates that products with improved product quality may be different products and, therefore, not comparable. Here lines 800-808 suggest that for some attributes, comparability can be claimed if non-inferiority criteria are met. • An edit is proposed to clarify what "When the CQA of interest is a mean value" means.	…"When the **[results for a]** CQA of interest **[are reported as]** a mean value"…
810-813	If the lots selected for the comparability study are not representative of your typical manufacturing process, the corresponding results will have limited meaningful interpretation, regardless of the particular statistical methodology applied.	We propose slight rewording for clarity.	~~If~~ **[T]**he lots selected for the comparability study ~~are not~~ **[should be]** representative of your typical manufacturing process ~~the~~ **[to ensure]** corresponding results will have

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Section & Line Numbers	Guidance text	Comment and, Where Applicable, Rationale for Proposed Change	Proposed Change
			meaningful interpretation, regardless of the particular statistical methodology applied.
815		We recommend adding additional statistical examples.	Add the following points: **[• Comparability of pre- and post-change lots may also be evaluated using Bayesian methods by constructing probability intervals for means or difference in means, as well as predictive intervals for future batches.** **• For quality ranges, various methods can be used to construct statistical intervals based on the distribution of the data (or the transformed data) such that the post-change results can be compared to expected values from the pre-change process.]**
VI. SPECIAL CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL PRODUCTS			
General comment (Lines 816-869)		• There is no guidance regarding planned changes to transportation, handling/preparation at a clinical site and/or the surgical procedure. Additional guidance, if "in scope" would be appreciated.	

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Section & Line Numbers	Guidance text	Comment and, Where Applicable, Rationale for Proposed Change	Proposed Change
		• Additional guidance regarding specific considerations for planned changes to transportation, handling/preparation at a clinical site and/or the surgical procedure would be useful.	
842-848	Both manufacturing changes introduced before combining the cells and scaffold and manufacturing changes introduced after combining the cells and scaffold (e.g., changes to the culture conditions, packaging, storage, or shipping) may have a significant impact on the overall biological activity and/or performance of the TEMP. Therefore, comparability studies for TEMPs should often include evaluation of the effect on DP quality even when manufacturing changes are made only to the scaffold or to the cells prior to combining these two components.	This appears to suggest that when introducing manufacturing changes to a TE product, two comparability evaluations (or more if a change is introduced to more than one component) are necessary. The practicality of this approach can become a challenge, particularly given the limited degree to which there is understanding regarding product quality, interactions between cells and scaffolds in vitro and host environment interactions with the DP post administration.	Additional guidance or examples for TE products.
VII. Communication with FDA			
877-880	Communication with the FDA can be sought either by requesting FDA comment on relevant information submitted in an IND amendment or BLA product correspondence, or through a formal meeting request (Ref. 15). The type of meeting used for such discussions depends on the stage	Please clarify which of the communication forms is most appropriate under which circumstances. Would a type D meeting be an appropriate way to obtain feedback on a comparability test protocol?	Communication with the FDA can be sought either by requesting FDA comment on relevant information submitted in an IND amendment or BLA product correspondence, ~~product correspondence~~ **[BLA supplement,]** or through a formal meeting request (Ref. 15)."

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	of the product lifecycle and the issues to be considered.		

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