American Society of Gene + Cell Therapy

November 13, 2023

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Comments for Docket No. FDA-2023-D-2436, "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry"

Dear Sir/Madam:

The American Society of Gene & Cell Therapy (ASGCT) welcomes the opportunity to comment on the draft guidance document *Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products*. ASGCT is a nonprofit professional membership organization comprised of 6,000 scientists, physicians, and other professionals working in cell and gene therapy (CGT) in settings such as universities, hospitals, government agencies, foundations, and biotechnology companies. Many of our members have spent their careers in this field performing the underlying research that has led to today's robust pipeline of transformative therapies. The mission of ASGCT is to advance knowledge, awareness, and education, leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

ASGCT commends FDA's attention to this topic, as comparability has become a recurring and inevitable hurdle for CGT developers. It is therefore important that FDA's guidance on the topic be clear, accessible to both experienced and new product sponsors, and flexible enough to respond to the varying situations sponsors may face. As the field grows and learns from its successes and challenges, guidance that is forward-looking and grounded in feasibility is especially needed.

Overall, the draft guidance seems to rely heavily on requiring statistical references for comparability studies while acknowledging that the number of lots available to complete such studies can be minimal. Because establishing statistical relevance with limited lots is very challenging, ASGCT recommends that the final guidance encompass alternative methodologies suggested below for

demonstrating comparability, particularly in smaller-scale studies or populations.

Sponsors continue to advocate for regulatory flexibility to respond to the unique nature of CGT product development. Several of ASGCT's members have experienced a more case-specific response during recent interaction with the regulatory Agency, but pointed out that this flexibility is not well reflected in the current guidance. The Society would like to respectfully highlight that apparent discrepancy and voice our concern that the draft guidance, as written, does not seem to leave much opportunity for sponsors to innovate and evolve their manufacturing technologies as development progresses.

Throughout the guidance, the need to demonstrate a lack of adverse impact on product quality, safety, and efficacy is emphasized. This may overestimate the current understanding, and abilities, of the field to predict and demonstrate the impact of planned manufacturing changes. Greater accommodation should be made to acknowledge that not all changes will result in the creation of a new product. The need for expedited communication from the Agency is always critical. Especially regarding changes that could result in the Agency's determination that the referenced change could result in a new product, therefore requiring a new IND. A determination such as this, could discourage sponsors from further development of the product and could lead to discontinuation of a promising product for patients in need. In addition, sponsors should have the opportunity to abstain from making proposed manufacturing changes if the Agency determines the changes will result in a full or partial Clinical Hold or require a new IND.

Manufacturing changes, supported by conclusive comparability studies, can be key enablers in the development of CGT products with implications across non-clinical, clinical, and CMC disciplines. While we are pleased to see sections of this guidance specifically discuss potential implications for non-clinical and clinical programs, we encourage the agency to address this topic holistically.

Communication with FDA

This draft guidance on comparability references the previous guidance, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry; Draft Guidance for Industry, September 2023." However, that guidance does not include Type D and INTERACT meetings, which are intended to focus on a narrow set of issues such as comparability. The Society seeks clarity on whether a sponsor could use Type D and INTERACT meetings to discuss comparability. The Society recommends the use of these types of meetings, particularly Type D meetings, to provide sponsors with a timeframe of when they may receive a response. Additionally, the Society would like to gain clarity on the type of comparability data that would be required for such a submission.

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In addition to these general comments, the Society respectfully requests that the following line edits to the guidance be considered:

I. Introduction		
Lines/Section/ Text Reference	Draft Guidance Text	Comment/Recommendation
N/A	N/A	N/A
II. Background		
Lines/Section/ Text Reference	Draft Guidance Text	Comment/Recommendation
46-49	"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." **Comment:** ASGCT suggests that it would be better to have guidance immediately following this sentence on how to address changes. Of importance, pre- and post-change products are not "different" products.	"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 considered comparable**. ~~**different products and, therefore, not comparable**~~"

54-58	Risk Assessment…"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. Otherwise, additional clinical studies may be warranted." **Comment:** ASGCT suggests that there is too much detail in the introduction. In some instances, analytical studies alone may not be sufficient. The risk assessment should inform comparability study design – analytical testing plan including in-process controls, release testing, side-by-side testing, characterization, and, if significant risks are identified, nonclinical or clinical studies.	~~**Risk assessment… "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. Otherwise, additional clinical studies may be warranted."**~~
74-75	"and some manufacturing changes without adequate comparability data may result in a clinical hold (21 CFR 312.42(b))" **Comment:** ASGCT recommends risk assessments to avoid deficiencies that could result in a clinical hold. Sponsors should be afforded the opportunity to decline implementation of a manufacturing change if they are informed that the implementation could result in a clinical hold.	"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."**
III. CONSIDERATIONS FOR THE MANAGEMENT OF MANUFACTURING CHANGES		

Lines/Section/ Text Reference	Draft Guidance Text	Comment/Recommendation
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." **Comment:** A robust framework for managing manufacturing changes is expected for GMPs, not just for CGT.	~~**"A robust framework for managing manufacturing changes is especially valuable for CGT products because of the complexity of these products and their manufacturing processes."**~~
99-101	"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." **Comment:** CPPs are often not in place in early phase investigational products and some changes may intentionally impact process parameters to introduce better control over CQAs.	"For investigational products, maintaining product quality by control of **manufacturing process and** CQAs ~~**and critical process parameters (CPPS) during**~~ **after** manufacturing changes is important for obtaining interpretable clinical study data that can support licensure."
A. Risk Management		
114-118	To achieve yield, scale, quality or other improvements, a process may be required to extensively overhaul unit operations. If no unit operation is the same from pre- to post- change, will expanded characterization support DS and DP comparability?	Propose to make clear that 1) additional characterization can be sufficient if unit operations are not identical, or 2) clarify that process improvement is a justification that unit operations which are not the same between processes are nevertheless equivalent (comparable) based on their analytical outputs.

126-129	"…additional process performance qualification studies…"	Manufacturing changes implemented in later stage clinical development may be required because clinical study designs use smaller numbers of patients and CMC changes require longer periods of time to implement, demonstrate comparability and become process qualified. Proposed change: provide guidance on whether CPV can be introduced during PPQ and be considered as supporting change management during BLA submission review
132-133	"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." **Comment:** ASGCT suggests providing a clearer definition of the word "extensive" in this specific context, as well as a list of examples of what is considered "extensive."	
143-147	"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 601.2(d))."	"For ~~both investigational licensed~~ 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 601.2(d)).”
156-157	“DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, or shipping conditions.”	“DP stability should be thoroughly assessed after changes to the container closure system, formulation, product concentration, **storage conditions** or shipping conditions.”
B. Stability and Delivery Device Compatibility		
172-177	“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.” **Comment:** Real-time long-term stability studies are routinely done, and they do not delay product development or implementation of the manufacturing change. ASGCT requests clarity on whether real-time stability data translates into needing a leading lot vs ability to project shelf life, which is common for investigational products early in development.	

169-172	"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." **Comment:** For investigational products, initial shelf life is often provisional with little to no long-term data at IND opening and is supported by accelerated or other stability data.	"Accelerated stability studies performed under stress conditions may be useful for identifying stability-indicating attributes, **evaluating temperature excursions, and trending analysis**, ~~**but**~~ **while** ~~**shelf life should be based on**~~ real-time stability data obtained at the long-term storage condition **are required for shelf-life setting.**"
C. Nonclinical studies		
183-185	"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." **Comment:** ASGCT requests additional information on why nonclinical studies may contribute to a demonstration of comparability. It is unclear why nonclinical studies are recommended.	
D. Clinical studies		
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	"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-**~~

	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." **Comment:** ASGCT suggests changing the verbiage to reflect that it will be insufficient to support a BLA because the FDA is offering to work with sponsors to avoid this situation. This is an introductory section followed by investigational and licensed products subsections.	~~**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."
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." **Comment:** Efficacy is studied during Phase 3. In reading further, the Society suggests deleting this sentence since it is redundant with the next paragraph.	"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 of the post-change product in clinical studies intended to provide substantial evidence of effectiveness 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	In addition, ~~**evidence demonstrating a prospect of direct benefit of a pre-change investigational CGT product to pediatric subjects, as required**~~ **the requirements** for **conducting** studies ~~**conducted**~~ in **children in** accordance with 21 CFR 50.52,

	of direct benefit with respect to the post-change product." **Comment:** This is unclear as written, and the Society recommends replacing the conclusion that "may not be adequate" to state that 21CFR 50.52 applies as well when children are part of clinical investigations	~~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." **Comment:** ASGCT suggests replacing "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~~."
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. We also recommend that you seek FDA's advice (section VII of this guidance) on the design of the pooled data analysis, preferably before conducting late-phase studies intended to demonstrate product effectiveness in support of a BLA."	"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 **based on comparability assessment**. We also recommend that you seek FDA's advice (section VII of this guidance) on the design of the pooled data analysis, preferably before conducting late-phase studies intended to demonstrate product effectiveness in support of a BLA."

IV. REGULATORY REPORTING OF MANUFACTURING CHANGE		
Lines/Section/Text Reference	Draft Guidance Text	Comment/Recommendation
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)."	**"For licensed products,** applicants 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		
267-269	"Some changes can fundamentally alter the design or nature of the product, resulting in a new product." **Comment:** Clarification to replace "some changes" to describe as intentional changes to alter product.	"Some Changes **~~can~~ that ~~fundamentally~~ intentionally** alter the design or nature of the product**~~, resulting~~ may result** in a new product.
273-276	Change in the cellular starting material of a cellular product (e.g., allogeneic vs. autologous donor; adipose-derived cells vs. umbilical cord-derived cells) 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 request clarity that cell lines, which have already been used in clinic, have an established safety profile, would be used on the same patient population and product (treatment), could be minimally gene edited and not need a new IND. Process optimizations that cause cell subpopulation shifts and are considered optimizations to improve the product profile should not require a new IND
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)"	**Protein-coding changes such as the addition of a domain or second transgene.**

	Comment: ASGCT suggests that it is preferable to specify the type of change instead of referring to "change to the sequence of the transgene."	
B. Reporting Manufacturing Changes to an IND		
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 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." **Comment:** ASGCT acknowledges, that it is a well-known challenge because sponsors typically have very limited data so it's 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, clinical data should be evaluated for suitability of using pre- and post- change product in phase 3.	"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 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		
N/A	N/A	N/A
V. COMPARABILITY ASSESSMENT AND REPORT		
Lines/Section/Text Reference	**Draft Guidance Text**	**Comment/Recommendation**
368-371	"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." **Comment:** ASGCT suggests that a pre- and post- change product not being comparable doesn't mean the post- change product is a "different" product. Regarding gene reconstitution, ASGCT would like to know if effectiveness is improved in a new proposed product (i.e. better transduction or potency) without any safety concerns, or is this still a different product? ASGCT would also like clarity on whether the Agency will consider addressing this with the adaptive clinical trial design via dose escalation studies or via surrogate animal or Organs on a Chip (OoC) models?	"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 **not** be considered ~~**a different product, and therefore**~~ incomparable ~~**to the pre-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." **Comment:** ASGCT requests the addition of text with updates to other relevant quality sections. Comparability reports are rarely submitted without updates to other relevant quality sections.	
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." **Comment:** ASGCT requests clarity on how comparability should be interpreted if a predefined criteria for additional product characterization is not met? Will the Agency provide recommendations for additional analytical characterization criteria, especially for early-stage assets where all product quality attributes may not be fully defined.	
A. Risk Assessment		
408-410	"The process of evaluating the risk of a manufacturing change for a CGT product is similar to	

	risk evaluation for other types of drugs, and the same tools can generally be applied." **Comment:** Novel technology to address the current bottlenecks associated with scaling cell therapies continues to be developed. Will the Agency consider the ability of new technologies to address technical limitations in scaling therapies as part of a holistic risk assessment framework for manufacturing process changes?	
419-421	"Transferring a manufacturing process to a new manufacturing facility is generally considered a major change that may require extensive comparability evaluation in addition to tech transfer…" **Comment:** ASGCT suggests providing 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/results are minimally acceptable.	
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."	"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."

438-440	"You should consider whether your risk assessment is constrained by gaps in product knowledge related to the type of change being proposed. Gaps in knowledge typically raise the level of risk and may necessitate a more extensive comparability study." **Comment:** The Agency should provide further clarity about risk and comparability based on gaps in product knowledge as it relates to the state of drug product development.	
453	"Your risk assessment should also inform the statistical approach to comparability. " **Comment:** It is well recognized that one of the significant challenges is limited data as stated on line 519.	*"Your risk assessment should also inform the statistical approach to comparability* ***when sufficient amounts of data are available****."*
B. Analytical Comparability Study Design		
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."	Proposed change: Method optimization is an ongoing activity through product development. Data that demonstrates an optimized method is the same for the purposes of its use in the process should be sufficient for the method's continued use. Testing retain 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) is a suitable option to demonstrate assay performance.
522-524	"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." **Comment:** The Agency should provide further clarity around risk and comparability based on gaps in product knowledge as it relates to the state of drug product development. For rare disease indications, it is known that there are limited lots to obtain a data set that has statistical power to evaluate manufacturing changes. The Agency should provide further guidance on how to establish comparability when statistical power cannot be achieved.	"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. **Sponsors are encouraged to submit comparability protocols to seek the FDA's feedback on study design ahead of executing studies.**
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 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."
638	"An equivalence approach is often appropriate for evaluating comparability of CQAs"	"**When sufficient data is available**, an equivalence approach is often appropriate for evaluating comparability of CQAs."
642	"Exceeding this margin would be interpreted as an adverse effect of the post-change manufacturing process on product quality." **Comment:** Even when margins are exceeded, it does not necessarily mean that there is an adverse effect of the post-change manufacturing process on product quality.	**"Exceeding this margin would be interpreted as an ~~adverse effect of the post-change manufacturing process on~~ impact to product quality."**
645-647	"A quality range approach evaluates whether the post-change quality results fall within a defined range. This range should often be narrower than the release acceptance criteria for those same quality attributes." **Comment:** ASGCT suggests that the quality range approach should leverage scientific knowledge to establish a particular attribute's range. Further clarity is needed on the defined range. When using the Quality range approach, it should be identified based on a scientific understanding of the potential impact of a change during the holistic risk assessment. This should be leveraged to define the range,	

	whether it is the same as the release acceptance criteria or not.	
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." **Comment:** ASGCT suggests that it may not be helpful to sponsors to design a comparability study by calculating the number of post-changes lots needed to design the study with sufficient power. The post-change lots are made for clinical supply, not for statistical analyses.	~~"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."~~
C. Analytical Methods		
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 you provide a tabular listing of the analytical methods ~~and testing sites~~ used in the comparability study.
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." **Comment:** ASGCT suggests this information is too detailed for submission. Method qualification/validation, stability studies, etc., 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."~~

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."	"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."
718-728	"At all stages of the product lifecycle, when changing an assay or transferring an assay to a new testing facility, you should perform a risk assessment for the assay change to determine if there is a potential impact on evaluation of product quality, including evaluations conducted in comparability studies." **Comment:** Assays must be properly transferred then they may be used for future comparability studies. Transferring assays doesn't impact previous data.	"At all stages of the product lifecycle, when changing an assay or transferring an assay to a new testing facility, you should perform a risk assessment for the assay change to determine if there is a potential impact on evaluation of product quality ~~**including evaluations conducted in comparability studies**~~."
D. Results		
N/A	N/A	N/A
E. Statistics		
742-748	"When designing comparability studies for CGT products, appropriate statistical methods should be used to determine if the pre- and post-change products are comparable. The statistical methods should be defined in the comparability protocol before executing the comparability study. Selection of a statistical approach to demonstrate comparability of	N/A

	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." **Comment:** ASGCT would like to mention that limitations may exist with small sample numbers. The Agency emphasizes the need to use statistical approaches throughout the document. The Society would also like to know if the Agency would address the use of scientific knowledge/rationale to select an appropriate statistical method during the holistic risk assessment and how to evaluate comparability with limited sample numbers.	
VI. SPECIAL CONSIDERATIONS FOR TISSUE-ENGINEERED MEDICAL PRODUCTS		
Lines/Section/Text Reference	**Draft Guidance Text**	**Comment/Recommendation**
N/A	N/A	N/A
VII. COMMUNICATION WITH FDA		
Lines/Section/Text Reference	**Draft Guidance Text**	**Comment/Recommendation**
877-879	"Communication with the FDA can be sought either by requesting FDA comment on relevant	"Communication with the FDA can be sought either by requesting FDA comment on

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	information submitted in an IND amendment or BLA product correspondence, or through a formal meeting request (Ref. 15)." **Comment:** ASGCT requests clarity on the Agency's preference regarding formal meeting requests versus informal communications.	relevant information submitted in an IND amendment or BLA ~~**product**~~ correspondence **supplement,** or through a formal meeting request (Ref. 15)."

Thank you for your consideration of these comments. ASGCT looks forward to continued collaboration with the Agency on issues critical to the development of, and manufacturing of CGTs. If you have any questions, please contact Margarita Valdez Martínez, Director of Policy and Advocacy, at mvaldez@asgct.org.

Sincerely,

David M. Barrett, J.D.

Chief Executive Officer